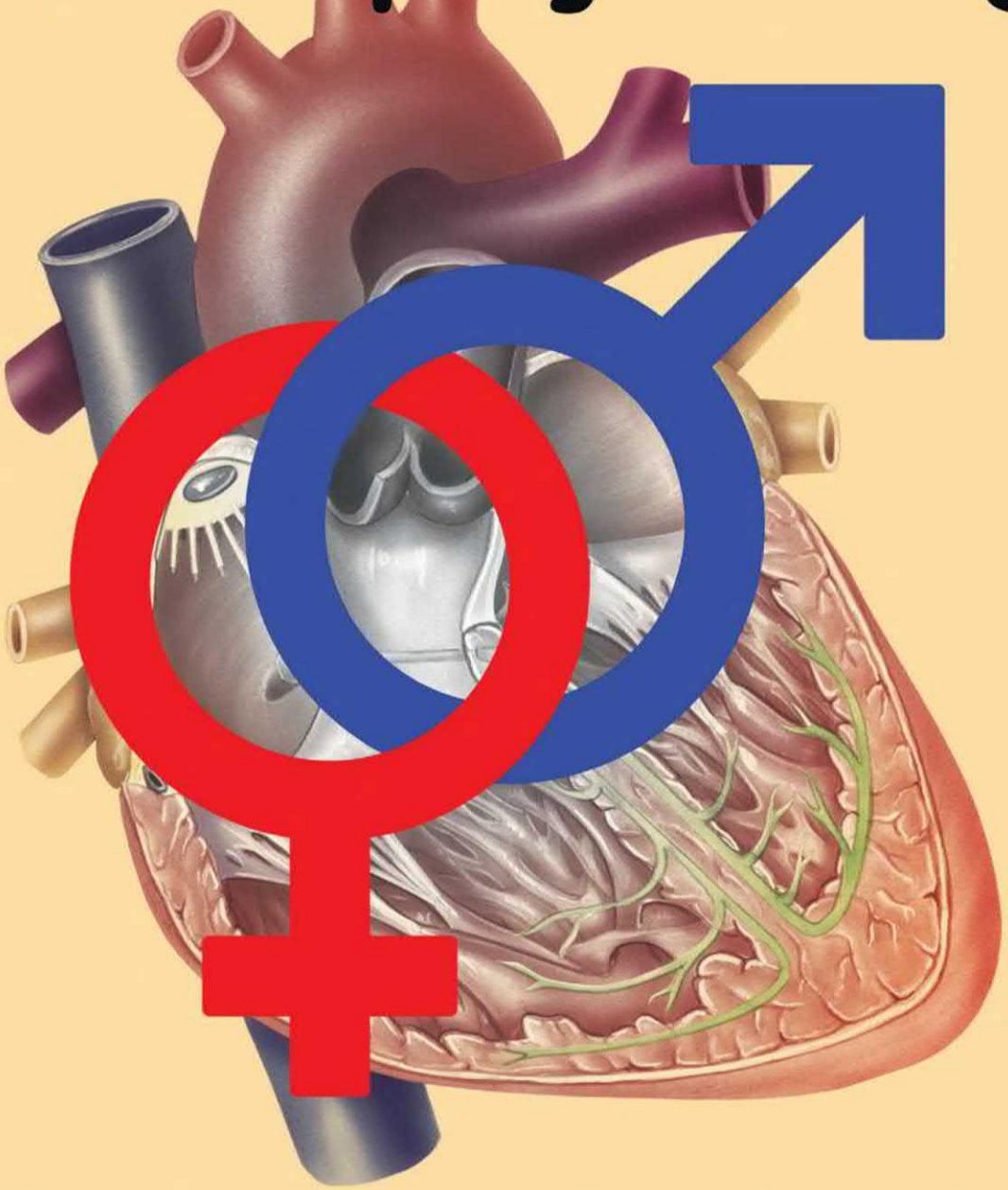
Edited by

Marek Malik

Sex and Cardiac Electrophysiology



Differences in Cardiac Electrical Disorders Between Men and Women

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Edited by

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To
Alice, Antonia, Timothée, Rebecca, Elizabeth,
Matthieu, and Susannah

Contents

Part VI
Channelopathies

Part VII
Drug-induced electrophysiology abnormalities

Part IX
Cardiomyopathies and inherited disorders

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Foreword

During the last decade, we have seen major steps to promote equality between men and women giving them the same rights, resources, opportunities, and protections in multiple areas.

However, men and women are not the same, physically and psychologically. That may result in different types and mechanisms of disease, their risk, and also their response to management.

It is important to increase our understanding of these differences to decrease disparity of care and to improve quality of life regardless of sex and race/ethnicity.

Already in 1993, the FDA Office of Good Clinical Practice called for representation of all genders in clinical trials, noting that women were often excluded from clinical trials limiting the understanding of women's health and the potential of response to therapeutic measure.

In the Western world, cardiac disease is the major cause of death among women underlining the necessity to be better informed about the specific differences in comparison with heart disease in men.

In recent years, we have seen growing awareness of those differences in incidence, type, complaints, and outcome of a whole range of cardiac diseases including acute and chronic coronary artery disease, heart failure, and cardiac arrhythmias, but a comprehensive comparison between men and women and its importance for correct management is still lacking in several of the different types of cardiac diseases.

This book is a great step in closing that gap, by discussing female−male differences in the genetic, basic, and clinical background of normal and abnormal behavior of cardiac electrophysiology in a range of different cardiac diseases. It tells us about their significance for diagnosis, treatment, and prognosis. It is an indispensable source of information for the physician taking care of the cardiac patient.

By using artificial intelligence, computational techniques, biobank data, and individualized genetic information, we are entering a new phase in healthcare ultimately allowing us to come to personalized medicine taking into account sex and race/ethnicity. This book will be of great help, not only by giving important practical information but also by indicating the necessity of more studies into mechanisms responsible for these gender differences and how to apply best management. I like to congratulate Dr. Malik and his coauthors with a beautiful book that comes at a time when it is very much needed.

Hein Wellens

Preface

The biological differences between women and men are obvious and range from chromosomal composition to physiology and anatomy with the most evident differences in reproductive organs. This is the basis for the whole well-known spectrum of congenital abnormalities, pathologies, and syndromes that affect only women or only men.

It is perhaps less obvious and not so appreciated that women and men differ also in the physiology of their nonreproductive organs and in the reaction to pathologies affecting nonreproductive organs and systems. While these differences have been known for much longer, their implications for clinical medicine started to be valued only during the last decades. Disturbing statistics appeared showing that in some medical fields, women, as compared to men, are less frequently receiving treatment based on advanced technologies and that clinical trials that form guidelines for day-to-day clinical practice are based on data with disbalanced proportions between women and men. The search for the reasons of these disparities continues and strategies for mitigating their negative consequences are being actively developed.

It also became apparent that increased awareness of the detailed differences between women and men in physiology, pathology, and clinical characteristics is needed in specific medical fields. This led to a spectrum of documents on these topics that were initiated by learned societies representing various medical subspecialties. One of these documents was the recent statement on sex differences in cardiac arrhythmia that was initiated by the European Heart Rhythm Association (EHRA) and developed by specialists under the chairmanship by Professors Cecilia Linde and Andrea Sarkozy. The work on this document made it evident that the present knowledge of the cardiac electrophysiology differences between women and men is so extensive that many important details cannot be included despite the 42 printed pages that EHRA devoted to the topic. The discussions of what can and what cannot be included just because of the permitted size of the text eventually led to an idea of including all the details in a dedicated book.

Similar to other authors of the EHRA document, I was very pleased when Elsevier accepted the proposal to publish such a book including not only topics that have previously been reviewed only briefly but also related topics that have not been considered when the EHRA document was composed. Consequently, I was able to group the individual chapters of this book into sections that range from the sex differences in normal physiological tissues and normal organs to sex specifics in pathologies and in the clinical approaches to the pathologies. As with every other topic of contemporary medicine, further and further notes could still be added. Nevertheless, I hope that this book is now sufficiently comprehensive and that it will offer useful detailed coverage of this important subject. The field of sex differences in electrophysiology is evolving and a number of chapters in this book contain suggestions for further development in both physiologic investigations and clinical studies. I thus hope that the research-oriented readers of this book will find useful inspirations in these suggestions.

As with every other multiauthored volume, I had to deal with the usual editorial dilemma between having this book sufficiently compact with numerous cross-references between different chapters and having the individual chapters suitable for stand-alone reading and study. Eventually, I concluded that a book of this size would likely serve as a reference textbook and that having individual chapters composed as stand-alone reviews of dedicated topics is preferable albeit it would lead to some acceptable chapter-to-chapter overlaps. Consequently, the readers are welcome to choose individual chapters according to their particular interests and specific needs. Needless to say, studying this book in its entirety will provide more comprehensive insight into the broader field of the sex specifics in cardiac electrophysiology as well as a deeper understanding of the links between different facets of these sex differences.

Superficially, the field of sex differences in cardiac physiology might be perceived as relatively narrow. Nevertheless, the reader of this book will immediately understand that the field contains so many special topics that the contents of this book are obviously beyond the depths of knowledge of any individual specialist. I was therefore pleased that the authors of the different chapters were kind enough to join me in this project. Without their

expertise, knowledge, and writing skills, this book would have never been produced. Each of them deserves my deep appreciation and thanks.

As this book originated from the work on the EHRA document, I am grateful to Cecilia, Andrea, and other authors of the document for their seminal encouragement in this book project. I am equally grateful to the Publisher for all the careful editing of the texts and for the meticulous production of this book. While my appreciation goes to the whole Elsevier team, I owe particular thanks to Ms. Sara Pianavilla who was responsible for the Editorial Office of this book. Without her kind help and support, my Editor's duties would have been next to impossible.

Finally, I need to express my sincere apologies to my family since my work on this book deprived them of many moments of my free time. Their support and kind understanding of my commitments to this book also deserve my deep thanks.

Marek Malik,
London, 2020

Part I

Introduction

Chapter 1

The distinction between the terms sex and gender

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Since this book is devoted to the differences between females and males, it seems appropriate to start it with the following terminological note.

In some research and other publications, it became almost customary to use the terms "sex" and "gender" interchangeably as if they were synonyms with the same meaning. Irrespective of whether the confusion of these terms is considered appropriate for presentation reasons, the assumption that both terms are equal is not correct. Both terms have very distinct and different meaning confirmed by both the Oxford and the Webster dictionaries [1,2].

Sex

The noun "sex" has two separate principal meanings of the same linguistic importance.

Firstly, it means the act of species reproduction. If applied to human beings, this meaning of the term also applies to any activity reminiscent of the act of species reproduction. A derived variant of this first meaning of the term also allows it to be used when referring to the externally visible reproductive organs.

Secondly, the term sex means the distinction between female and male individuals defined by their genetic and biological differentiations. In *Homo sapiens*, similar to other mammal species, the biological definition is based on the combination of sex chromosomes with females and males defined as having XX and XY combinations, respectively.

It became customary to extend this distinction of biological sex differentiation also to cases of chromosomal abnormalities. Thus, for instance, because of the external appearance and other biological properties, the sex of Turner syndrome individuals is categorized female and the sex of Klinefelter syndrome individual as male. Nevertheless, these customary extensions of the biological term sex are not necessarily correct. It should be recognized that in biological descriptions of these and other chromosomal abnormalities, the sex distinction to females and males might be misplaced and that individuals with undetermined sex exist, as already recognized in the legislature of some countries [3].

Thus, as far as the distinction between females and males is concerned, the term sex is a biological characteristic that (in *H. sapiens* and other mammals) applies to each individual separately and is defined objectively.[1]

Gender

The term "gender" is primarily a grammatical term meaning the distinction of different classes of nouns and pronouns that follow different grammatical rules of inflections in their declension and other expression forms. While this grammatical concept is practically absent in English, it is well adhered to in other languages. In Latin (and consequently in many other derived languages), masculine, feminine, and neutral genders are distinguished. This potentially leads to a mix-up with the biological sex differentiation. Nevertheless, it is rather misplaced. There is little logic in the gender of nouns that lack any biological sex, e.g., the word for a theater is neutral in German (das Theater) and masculine in Russian while having almost identical pronunciation (Театр—as written in the Russian alphabet). Other languages also use very different structures. For example, the African language Supyire has five different genders for humans (also including the elephants), big things (including all other large animals),

1. For the sake of completeness, it should also be added that the term "sex" might also be used as a verb, meaning the processes of either the differentiation between biological sexes (e.g., "sex the fish in this pond") or arousing the desire in copulation activities, or, in a figurative form, making something more interesting (e.g., "the report has been sexed up").

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small things, collectives, and liquids; and an Australian language contains a special gender for vegetables (and as the language acquired expressions for more modern objects, a new word for an airplane now belongs to the vegetable gender), and so on [4]. Hence, the notion that the grammatical distinction of genders follows the same structure as the biological distinction of sexes is false and unfounded.

The other but secondary meaning of the term gender expresses the cultural, behavioral, and/or psychological characteristics typically associated with female or male sex. This includes also identification and self-identification with behavioral and psychological characteristics attributable to female or male sex. Nevertheless, this meaning of the term is not only binary but also denotes a range of identities that do not correspond to previously established ideas of female and male distinction.

Hence, as far as the distinction between females and males is concerned, this secondary meaning of the term gender is not individual but defined by societal position and by perception of such a position. It is not absolutely given but is declarative and potentially self-declarative.

Distinction of the terms

Thus, when speaking about the distinction between females and males, the term "sex" relates to a biological characterization, while the term "gender" expresses societal position and interpersonal classification.

As already stated, the term "gender" has frequently been used in scientific publications when dealing with sex differences and when the term "sex" would have been more appropriate. The reasons for this can only be speculated on. Perhaps, since the term "sex" also refers to the sexual intercourse the discussion of which is taboo in some but not in other societies, the term gender might have been perceived as more acceptable as far as public relations are concerned. Nevertheless, at present, the described definitions and the distinctions of these terms are well understood.

Medical literature is not the only field in which the sex and gender classifications are potentially confusing. Since the gender distinction between female and male (and other) societal strata might be self-declarative, there are transgender individuals in whom the gender identity does not correspond to the biological sex. This leads to occasionally heated discussions, for instance, those of whether the female/male distinction in competitive sports should be based on sex or on gender [5].

Nevertheless, the correct and careful distinction between the sex and gender classifications is important for proper understanding of the facts. For instance, if the lower participation of women in clinical trials is contributed by their being biologically more determined to avoid risk and the unexpected, the difference is sex-based. If, on the contrary, researchers running clinical trials are less willing to enroll women because they are perceived to be less cooperative and/or more difficult to follow, the erroneous and skewed trial population is based on gender differences. Likewise, the terms sex discrimination and gender discrimination should not be used interchangeably. Sex discrimination in modern medicine exists. It includes application of evidence-based stratification limits derived from studies conducted predominantly in men also to women, despite the knowledge of the biological sex differences. Medical gender discrimination is hopefully much rarer and, as an example, includes cases when women are deprived of appropriate treatments because they are perceived to be less worth the expense.

All authors of chapters in this book were asked to adhere to this terminological distinction.

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Chapter 2

The biological basis of sex and its role as a determinant of myocardial function in health and disease

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What is sex(ual reproduction) good for?

Meiosis is producing genetic diversity

Reproduction is an essential characteristic of life and a vital element for a species to ensure survival and to evolve and adapt to a constantly changing environment. At the cellular level, reproduction is achieved through mitotic divisions, which, in the majority of cases, results in the generation of two identical daughter cells (Fig. 2.1). At the organismic level, most eukaryotic species are sexually reproducing, and this requires the presence of two sexes, a female, which produces eggs, and a male, which produces sperm. For sexual reproduction to occur, the diploid chromosome set, which is normally present in all somatic cells, will be reduced to its haploid level with the help of the two meiotic divisions. Meiotic divisions are special and only occur in germ cells within the gonads. Apart from serving the essential purpose of reducing the set of chromosomes from its diploid (2n) to its haploid state (n), another very important aspect, and the main reason that sexual reproduction prevails in eukaryotes, is genomic recombination.

Genomic recombination during meiosis is achieved by three processes:

- crossing over, which occurs during prophase of the first meiotic division and involves the exchange of chromosomal material between homologous chromosomes.
- random segregation of parental chromosomes during meiotic divisions.
- fusion of two haploid gametes to produce a diploid zygote containing one chromosome set of parental and maternal origin, respectively.

Thus, while offspring produced by sexual reproduction is related to each parent, each individuum produced in this way becomes genetically unique and is different from any other offspring from the same parent. Meiosis as a prerequisite for sexual reproduction and fertilization is therefore a major driver of genetic diversity in a population.

Reproduction strategies

The vast majority of eukaryotes reproduce sexually, however, a significant number of species alternate between asexual and sexual reproduction, an ability which is also known as heterogamy. A prominent example is the freshwater crustacean *Daphnia* (water flea), which reproduces asexually in spring to rapidly populate freshwater ponds [1]. Environmental changes are often triggering a change in the mode of reproduction. The slime mold *Dictyostelium* multiplies via mitotic divisions under favorable environmental conditions and switches to sexual reproduction, when food becomes limiting [2]. Another famous example is the generation of male bees, which only develop from nonfertilized eggs, while fertilized eggs produce females [3]. Thus, plenty of species alternate between sexual and asexual reproduction and some even reproduce parthenogenetically (without fertilization). These species are not only found among invertebrates but are also present in vertebrates, including sharks [4], lizards [5], and birds [6]. Of course, a species that reproduces by obligate parthenogenesis is in danger of reduced genetic diversity, which potentially leads to decreased fitness of the offspring. For some species, it could however be an advantage to reproduce asexually to populate a novel habitat, an example

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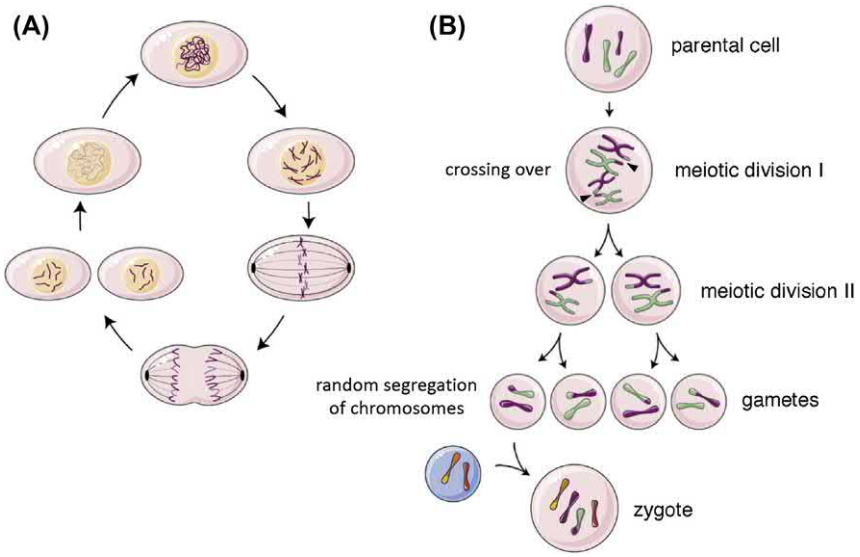

FIGURE 2.1 **Strategies of reproduction.** (A) Identical cells are produced by mitotic division. Most divisions within an organism are mitotic divisions. (B) Meiotic divisions are a special form of division and only executed by germ cells and at the basis of sexual reproduction. There are several differences between mitosis and meiosis: (1) meiotic divisions entail two consecutive rounds of cell division; (2) genetic material is interchanged between chromosomes; (3) parental chromosomes are randomly distributed between gametes; and (4) fertilization generates zygotes with recombined genetic material. Thus, the product of meiosis and fertilization is the genetically unique individuum. In contrast, mitotic divisions produce offspring, which is genetically identical to the parental generation.

would be the already mentioned water flea to populate a novel area almost twice as fast as it would if offspring is generated by sexual reproduction.

Animal species that only reproduce asexually are rare. One well-studied example is the genus *Bdelloid*, which are sweet water rotifers and all individuals are females [7]. Asexuality evolved in these animals millions of years ago and has persisted since. How an animal can survive without sexual reproduction for such a long period of time is a puzzle for evolutionary biologist. But even in *Bdelloid*s, each individuum is not genetically identical. Genomic diversity is achieved through horizontal gene transfer, i.e., the genome of these animals contains many foreign genes from other species [8].

Sex-specific imprinting

If parthenogenesis is present in many invertebrates and even in around 100 vertebrate species, the question arises why then pathogenesis is not present in mammals and in particular not in humans? The lack of uniparental offspring in case of mammals is due to the presence of sex-specific imprinting, which involves epigenetic modifications (most often methylation). These chromosomal marks are laid down during spermatogenesis and oogenesis (Fig. 2.2).

Paternal and maternal chromosomes differ in their methylation pattern [9]. Only zygotes, which are the result of the fusion of sperm and oocyte, develop normally and display a balanced gene expression level. While gynogenotic and androgenotic embryos (with two maternal or paternal sets of chromosomes, respectively) can be experimentally produced, both embryos are abnormal and do not develop further than the 25 and 5 somite stage, respectively. These embryos either consist mainly of embryonic (gynogenotic) or placental (androgenotic) cell lineages, respectively (Fig. 2.2). The reason for the presence of imprinting in mammalian embryos has not been fully elucidated, but probably is related to placentation. There are obviously the needs to balance the amount of material utilized for placenta development and for the embryo. There are around 100 genes, which are known to become imprinted [9]. In addition, however, a large number of miRNAs and lncRNAs are also subject to imprinting suggesting that it actually affects a considerable part of the genome. Disturbance of imprinting has been associated with a number of syndromes (Prader–Willi syndrome, Beckwith–Wiedemann syndrome, and Angelman syndrome) [10]. Some of these patients also develop cardiac phenotypes such as congenital heart disease [11] or left ventricular dysfunction [12].

A prominent example of a gene cluster, which is subjected to imprinting, is *IGF2/H19*. In most somatic cells, both genes are imprinted in a reciprocal manner, the paternal chromosome expresses *IGF2* and the maternal chromosome transcribes *H19* [13]. The *IGF2* gene encodes an insulin-like growth factor and serves an important function as a growth regulator, while H19 encodes a long noncoding RNA, which is not essential for development. While initially it was thought that imprinting would

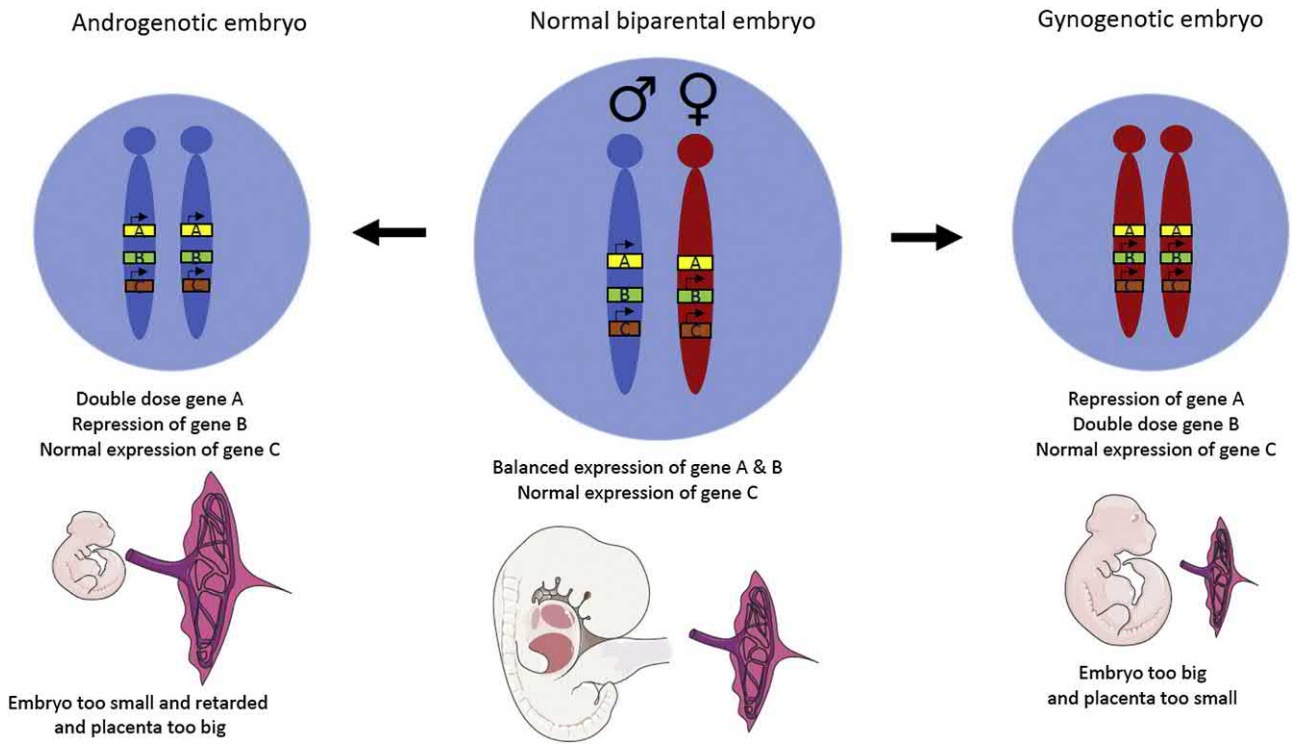

FIGURE 2.2 **Parental origin–specific gene imprinting.** In the center, a cell is depicted, which displays a single chromosome pair, which is of maternal (red) or paternal (blue) origin. Gene A and gene B are subject to sex-specific imprinting. As a result, gene A is transcribed exclusively from the paternal allele, while gene B is transcribed from the maternal allele. The majority of genes (such as gene C) are transcribed from both alleles. Uniparental embryos (androgenetic or gynogenetic) are depicted to the left and right and develop abnormally due to abnormal imprinting causing deregulated gene expression. The resulting embryos develop abnormally and are either too small (androgenetic embryo) and mainly consist of extraembryonic material or too big (gynogenetic embryo) and produce insufficient extraembryonic tissue. In both cases, embryonic development terminates early. Imprinting is the reason for the fact that parthenogenesis (uniparental offspring) does not exist in mammals. *Adapted from Bartolomei MS, Ferguson-Smith AC. Mammalian genomic imprinting. Cold Spring Harb Perspect Biol 2011;3(7).*

modulate placenta development and embryonic growth, it is now clear that imprinted genes are acting in a diverse functional context [14]. To complicate things, there is evidence that imprinting can be lost in a tissue-specific manner allowing transcription from both alleles or a switch of the allele, which gets utilized. An example of an imprinted gene cluster expressed in the heart is represented by the genes *DDC* and *GRB10*. *DDC* encodes a protein involved in neurotransmitter metabolism, while GRB10 is an adaptor protein involved in tyrosine kinase receptor signaling. A transcript variant, Ddc_exon1a, is exclusively transcribed in the heart from the paternal allele, while the reverse is true for *GRB10*, which is only transcribed from the maternal allele [15].

Why sexual reproduction prevails?

We have seen that reproduction in the animal kingdom is diverse and species have adopted alternative strategies. While both invertebrate and vertebrate species exist that transiently reproduce asexually, sexual reproduction prevails in most species. This leads immediately to the question why sexual reproduction is favored, as sexual reproduction is very inefficient? As an individuum, a lot of time and energy has to go into finding and attracting a mating partner, successfully copulating and fighting off any competitor. Moreover, parthenogenetically producing offspring will involve the entire population, while in case of sexual reproduction, 50% of the population will not produce any offspring. Thus, based on these numbers, asexual reproduction should prevail, but it does not. Sexual reproduction leads to genetic diversity, and this genetic diversity is thought to be a protective mechanism to successfully fight parasitism and other competing species [16].

Sex determination and hormonal control

Chromosomal sex determination

Surprisingly, despite that sex is such an important factor in the evolution, sex determination is extremely diverse, and mechanisms are not conserved, even in closely related species. In mammals, the sex of the organism is determined by two sex chromosomes (X and Y). Sperm cells can either carry an X or Y chromosome and fertilize eggs, which carry

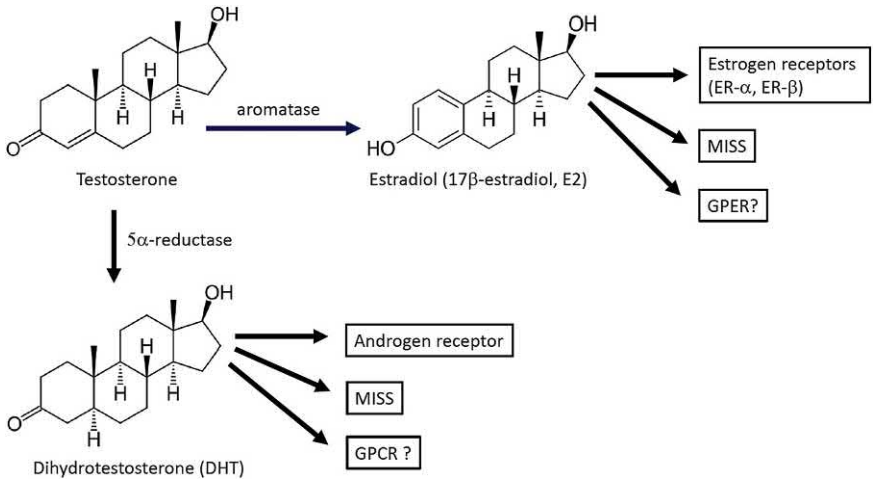

FIGURE 2.3 **Sex hormones and their receptor.** Male and female steroids are derivatives of cholesterol. Testosterone and dihydrotestosterone are the male sexual hormones. Both steroids bind to the androgen receptor (AR) to induce changes in gene expression and to trigger male development. The female hormones constitute a larger group of estrogen-like steroids of which 17β-estradiol (E2) is most potent and prevalent. Aromatase catalyzes the conversion of testosterone into E2. In both sexes, all three sex steroids are present, albeit at vastly different concentrations. E2 binds to the estrogen receptors ERα and ERβ and testosterone and DHT bind to the AR. Ligand binding triggers nuclear translocation and changes in gene expression. Palmitoylation of ERα, ERβ, and AR is causing plasma membrane localization of the steroid receptors and recruitment into caveolae. These modified receptors mediate membrane-initiated steroid signaling (MISS). Non-genomic responses are potentially mediated by the G-protein coupled receptors GPER in case of E2 and several candidate GPCRs in case of DHT, respectively (see the section "Signal transduction of sex steroids") for a further discussion of this topic. *ER*, estrogen receptor; *GPCR*, G protein−coupled receptor.

an X chromosome. The offspring is therefore either heterogametic (X/Y) triggering male development or homogametic (X/X) and become females. A single gene on the Y chromosome, sex-determining region Y (*SRY*), determines male development. A similar gene is not known for female development, which is thought to represent the default state. However, female masculinization has been observed in mutant mice with an ablation of the signaling factor Wnt4 [17]. This effect is probably caused by the suppressive function of Wnt4 to prevent differentiation of testosterone-producing Leydig cells during ovarian development. Interestingly, female patients carrying a *WNT4* missense mutation develop gonadal dysgenesis and both vagina and uterus are absent [18]. During early development, the gonad is sexually indifferent and only subsequent to the production of sex hormones (Leydig cells producing testosterone in males and Theca cells producing estrogen in females) gonadal sex differentiation will be triggered (Fig. 2.3).

As mentioned before, sex determination is surprisingly diverse and thus many reptiles and fishes do not rely on sex chromosomes and a sex-determining gene but rely on environmental cues. Sex in egg-laying reptiles (turtles, lizards, crocodiles) is temperature-controlled. The mechanism is probably related to the metabolism of male and female sex steroids. Testosterone can be rapidly converted into estradiol through the enzyme aromatase (Fig. 2.3). Temperature in the nest will therefore control aromatase activity, determine the relative testosterone and estradiol levels and thereby directing sexual differentiation of the offspring [19].

The X chromosome is a big chromosome containing 155 Mb of DNA and about 1100 genes. Most genes present on the X chromosome have no relevance for sex determination and sexual differentiation. The Y chromosome was long thought to be a genetic wasteland. Compared to X chromosome it is a rather small chromosome and contains only 568 genes of which only 27 are actually protein coding [20]. 14 of these genes are considered to be testis-specific, while 9 are ubiquitously expressed. Most genes present on the Y chromosome are involved in male sex determination and spermatozoa differentiation [21].

The sex-determining region of Y-Gene (*SRY)* encodes a Sox-box transcription factor [22]. SRY in complex with SF1 induces the upregulation of Sox9, a structurally related Sox-box transcription factor. Sox9 is responsible for the testis-specific differentiation of the bipotential gonad. SRY can be substituted by Sox9 provided that it is appropriately expressed in the male gonad, which can be achieved with the help of the WT1 promoter [23]. While the *SRY* gene transferred to X chromosome is able to induce a male phenotype in homogametic (XX) transgenics and *SRY* null mutants are females, the sperm cells of SRY transgenics are not able to differentiate [22]. In mice, a second gene termed *EIF2s3y* is also required to generate mature sperms. Thus, a transgenic animal, which lacks an X chromosome but contains copies of SRY and *EIF2s3y*, produces immotile sperm, which to induce fertilization after injection into oocytes [22].

The male sex-determining gene, SRY, is expressed not only in the testis but also in the brain, kidney, adrenals,

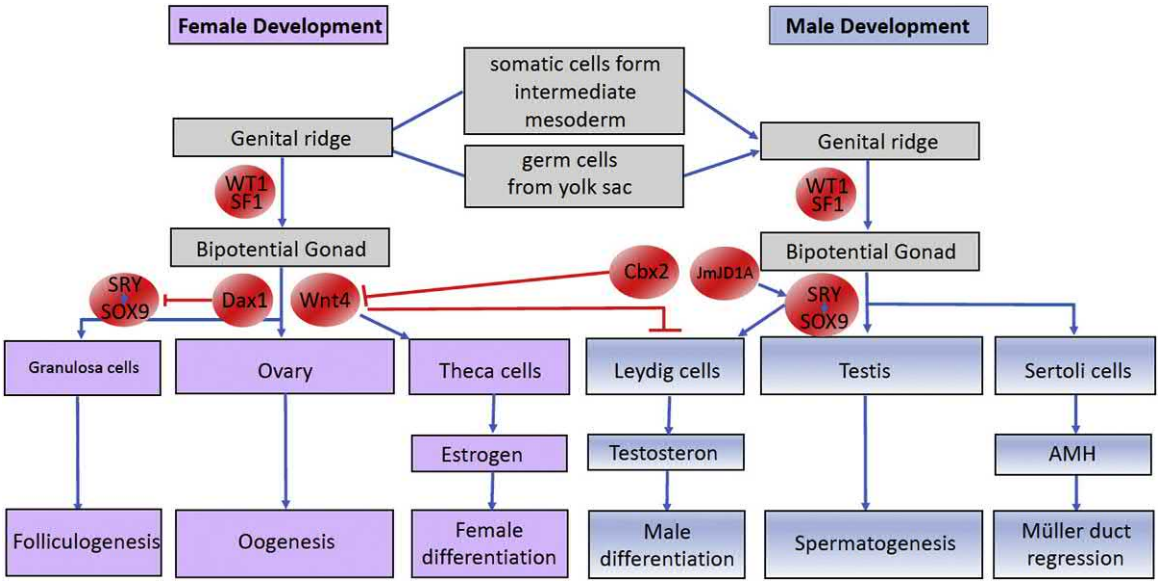

FIGURE 2.4 **Molecular pathways that govern female and male sexual differentiation.** Sexual differentiation goes through an early phase of bipotential gonad development, which is under the control of WT and SF1. At this time, germ cells are kept outside of the embryo proper and are localized in the yolk sac. They migrate to the developing gonad once sexual differentiation has started. Male development is triggered by JmJD1A, a chromatin remodeling factor responsible for the induction of SRY. SRYs, an SOX-box transcription factor localized on the Y chromosome induces, the expression of SOX9, which initiates male gonadal development and also induces the differentiation of Leydig and Sertoli cells, which are producing the anti-Müller hormone (AMH) and testosterone, respectively. Female development is controlled by WNT4 and DAX1. *DAX1* is X-linked. Its role is dosage sensitive as a single copy (as in males) promotes testis development, while at double dosage (as in female embryos), testis development is blocked and female gonadal development is promoted. WNT4, which is under negative control by the chromatin remodeling factor Cb2, promotes female gonadal differentiation and the production of estrogens by Theca cells and represses the production of testosterone-producing Leydig cells.

esophagus, and adipose tissue. Interestingly, in case of the spontaneously hypertensive rats (SHRs), when crossed with normotensive Wistar rats, the sex of the SHR rat determines the blood pressure in male offspring [24]. A male SHR rat produced offspring with significantly higher blood pressure compared to SHR mothers, suggesting that the Y chromosome contains a blood pressure determinant. A strong candidate is the *SRY* gene itself, which in rats, unlike humans, is present in multiple functional copies [25]. SRY, in synergy with the androgen receptor (AR) and in a testosterone-dependent manner, regulates a set of genes involved in blood pressure regulation (i.e., the renin–angiotensinogen aldosterone system, RAAS). Sequencing revealed the presence of an *SRY3* gene in the SHR, which contains a proline to threonine substitution. Experimental delivery of the SRY3 variant into the kidneys of normotensive rats leads to a rise in blood pressure [26]. Unfortunately, the translatability of these findings is uncertain, as the rat and human SRY proteins are very different proteins. Despite this, human SRY modulates RAAS gene expression when transfected into cultured cells [27]. Currently, there is a strong Y-chromosomal association with blood pressure control in rats, while only weak links have been found in case of humans.

Sex determination is not fully irreversible, and stabilization and maintenance involve epigenetic mechanisms in human and mice. Activation of SRY expression requires demethylation, which is executed by the histone demethylase *JMJD1A* (Fig. 2.4). Male mice with a lack of *JMJD1A* display a high frequency of sex reversals [28]. Furthermore, lack of the chromatin remodeling protein chromobox protein homologue 2 (Cbx2) causes hypoplastic gonad development and high frequency of male-to-female sex reversal [29]. Significantly, a patient with male-to-female sex reversal carried a mutation in *CBX2*. It is thought that CBX2 may mainly function as a silencer of the female pathway and thereby promoting male differentiation.

X-chromosome inactivation

Females have two X chromosomes, whereas males have only a single X chromosome. This chromosomal imbalance between sexes triggers the epigenetic process of X-chromosome inactivation (XCI) and involves transcriptional silencing and heterochromatinization of one of the X chromosomes in female embryos [30]. In the murine embryo at the four to eight cell stage, the paternal X chromosome undergoes X-inactivation. After implantation of the blastocyst, epiblast cells transiently reactivate the inactivated X chromosome. Biallelic X-linked gene expression is rapidly terminated via a second wave of XCI, which affects both the paternal and maternal X chromosomes, which are randomly chosen for inactivation. In the human preimplantation embryo, the early phase of XCI is substituted by a net reduction of X-linked gene

expression, which is also termed as X-chromosome dampening [30]. A long noncoding RNA, Xist which is encoded in the X-inactivation center of the X chromosome, is required for XCI. During initiation of XCI, Xist recruits a diverse set of proteins that establish heterochromatin formation of the X chromosome, also known as the *Barr body*. Conditional ablation of *Xist* in the early embryo affects embryo implantation and is therefore embryonic lethal. If however, ablation, of *Xist* is confined to the embryo proper, some animals develop normally and die postnatally after 1 month [31]. It is thought that some of the functions of Xist can also be executed by other lncRNAs.

XCI will lead to random inactivation of one of the two X chromosomes in tissues of the female body. Since the process is random and will happen sometime during embryogenesis, tissues in the adult are mosaic, i.e., neighboring cells are genetically different due to the inactivation of one or the other X chromosome. This fact has important consequences for sex-linked genetic diseases such as Duchenne muscular dystrophy (DMD) and its milder form Becker muscular dystrophy (BMD). Both forms of muscular dystrophy are X-linked and due to mutations of dystrophin (*DYS*), a cytoskeletal gene, which is located on the X chromosome [32]. While in DMD, dystrophin is absent, in BMD some partially functional dystrophin is still present.

DMD mainly affects boys, while females usually display only a mild phenotype due to presence of the mutant allele only in a fraction of the cells. Since skeletal muscle cells are fusing to form myotubes, dystrophin is produced in sufficient amounts to protect the cells of developing the disease. Dystrophin is involved in the formation of the dystrophin-glycoprotein complex present in heart and skeletal muscle cells linking matrix proteins of the basement membrane with the cytoskeleton [33]. Dystrophin not only provides muscle cells with structural integrity but may also be involved in signaling important for cell protection and vascularization [34]. *DYS* is located on the X chromosome and therefore subjected to XCI. DMD/BMD female carriers are usually asymptomatic, although several studies report that a small fraction (2.5%−7.8%) may manifest skeletal muscle symptoms. Also cardiac phenotypes such as dilated cardiomyopathy (DCM), characterized by significant left ventricular dilatation and decreased shortening fraction, have been described in female carriers [35]. A recent analysis of XCI suggests the presence of a skewed (nonrandom) XCI, which preferentially inactivated the normal *DYS* allele [36]. Random XCI will only produce mild symptoms in female carriers. In contrast, moderate to severe phenotypes are associated with skewed XCI. The underlying mechanism, which triggers biased XCI, is presently unknown. Skewed XCI in case of DMD or BMD mutations represents therefore a prototype of a novel sex-specific disease mechanism.

Not all genes on the X chromosome are inactivated by XCI. Some genes escape inactivation and are expressed from both X chromosomes, which therefore results in an increase in gene doses between sexes [37]. It is estimated that up to 15% of the X-linked genes in men and 3% in mice are incompletely inactivated and remain biallelically expressed. At present, it is not known whether escape of X-inactivation does play any major role in cardiovascular disease (CVD).

Sex hormones, receptors, and signaling pathways

Synthesis of sex steroids

Sex steroids are synthesized by a stepwise modification of cholesterol. In the male body, both testosterone and dihydrotestosterone (DHT) are present. DHT is produced from testosterone by 5α-reductase (Fig. 2.3). Around 10% testosterone in the male body is converted into DHT, which however has the stronger biological effect and triggers sexual differentiation in male and females during puberty. Both male hormones are present in females but normally at a much lower concentration than in males. Steady-state physiological levels of testosterone in males range between 10 and 30 nM and 0.6−2.5 nM in females [38]. In females, testosterone is converted into E2 with the help of aromatase. Secretion of E2 is pulsatile and fluctuates during the menstrual cycle (100−600 pg/mL). Levels increase almost 30-fold during pregnancy (17 ng/mL) [39]. However, in postmenopausal women, the E2 level drops to 5−20 pg/mL, which is similar to what is found in men of similar age. Thus, during lifetime, the female body is exposed to vastly different E2 levels.

Sex hormones are not only produced in the gonads but also locally in many organs such as bone or fat tissue. Expression of the aromatase encoding cytochrome P450 family 19 subfamily A member 1 gene (*CYP19a1*) has been detected in human and rodent pericardial fat tissue, atrial appendage, and ventricle displaying an age-dependent increase in expression [40]. Aromatase is expressed at higher levels in females than in males. Feeding mice with a high fat diet leads to an increase in pericardial fat tissue and consequently in an increase in aromatase expression. A correlation between aromatase level and the incidence of atrial fibrillation was observed. Mouse mutants carrying a loss-of-function allele of the *CYP19A1* gene cause an aberrant development of uterus and ovaries in females, while male mice appeared to be grossly normal [41].

Receptors for sex steroids

Testosterone and DHT are recognized by the AR, while two estrogen receptors (ERα and ERβ) bind E2. Both estrogen receptors are made up of the same general

structure; however, they differ in their DNA-binding and ligand-binding domains, which probably forms the basis for differences in their transcriptional activity [42].

Loss of the ERα gene (*Esr1*) is associated with female infertility due to underdevelopment of ovaries and uteri and abnormal sexual behavior, while ERβ (*Esr2*) null mutants display subfertility due to reduced ovarian function [43]. Males lacking *Esr1* were also infertile and displayed an atrophy of testes and dysmorphogenesis of the seminiferous tubule suggesting that low levels of E2 are also required for male sexual differentiation. Expression of ERα and ERβ was studied in rat and murine cardiac myocytes. Surprisingly, only ERα was found to be expressed in cardiac myocytes, while ERβ was absent [44]. However, other studies not only demonstrated the presence of both receptors in rodent myocytes but also their functional activity [45–47]. Estrogen receptors are also found in neonatal rat cardiac fibroblast [48]. Loss of *Esr1* affects cardiac metabolism causing a reduction in glucose uptake [49]. Loss of *Esr2* is causing hypertension and myocyte disarray, disruption of intercalated disks, an increase in the number and size of gap junctions, and a change in nuclear structure and in nuclear lamin A/C expression [50]. Both ERα and ERβ are expressed in the heart and their expression is modulated by E2 [46]. Two E2 target genes, which also display estrogen response elements and bound by ERα, are *Nppa* (encoding ANF) and *Gja1* (encoding Cx43) [51]. Study of *AR* null mutant mice was more complicated as the *AR* gene is located on the X chromosome. Thus, male mice carrying the *AR* null mutation were infertile and a stable mouse line could not be established. A conditional allele allowed to study the consequences of an *AR* null mutation, which causes a feminization of the external genitalia, while male reproductive organs were absent, however, female organs were not present [52]. Like the estrogen receptors, AR is expressed in many cells of the cardiovascular system including cardiac myocytes [53], endothelial cells [54], and vascular smooth muscle cells [55]. Testosterone and DHT given to cardiac myocyte cultures are inducing a hypertrophic response including increased protein synthesis and *Nppa* expression [56]. Androgen effects on cardiac myocytes have also been studied in *AR* null mutant mice [57]. These mice, when infused with angiotensin II (AngII), display a reduced hypertrophic response compared to wild-type (WT) mice. However, both left ventricular function and cardiac fibrosis were worsened suggesting that AR signaling is beneficial under these pathological conditions.

Signal transduction of sex steroids

The nuclear hormone receptors AR, ERα, and ERβ are kept in the cytoplasm by binding to heat shock protein 90 (Hsp90) [58]. Binding of the lipophilic hormones to their receptors causes a breakup of the inhibitory complex, dimerization of receptor monomers, and transport of the ligand receptor complex into the nucleus, where a large number of target genes are recognized by the ligand–receptor complex (Fig. 2.5).

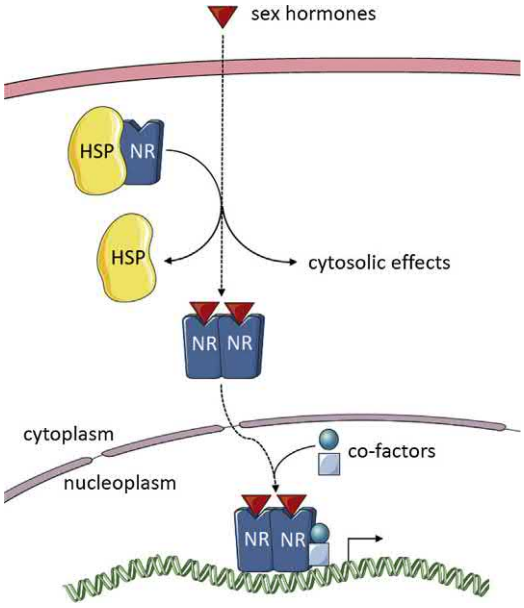

FIGURE 2.5 **Nuclear receptor signaling.** Sex hormones are lipophilic and diffuse through the plasma membrane. Sex hormone receptors belonging to the type I class of nuclear receptors are kept as monomers in the cytoplasm through interaction with the chaperone HSP90. In response to ligand binding, the protein complex dissociates and the nuclear receptor dimerizes and is transported into the nucleus. Here, tissue-specific transcription factors and cofactors associate with the nuclear hormone receptor and bind to enhancers of target genes and ultimately activate transcription. *Adapted from Sever R, Glass CK. Signaling by nuclear receptors. Cold Spring Harb Perspect Biol 2013;5(3):a016709.*

However, evidence has accumulated that the time required for a transcriptional response cannot explain some of the physiological responses that are observed in seconds after the addition of sex steroids [59,60]. Search for the receptor(s) mediating these short term nongenomic responses has lead to the identification of G protein–coupled receptors (GPCRs), but data of their physiological function in steroid signaling are still uncertain [61]. Four proteins have been identified as potential acutely acting ARs, i.e., G protein–coupled oxo-eicosanoid receptor 1 (OXER1) [62], G protein–coupled receptor family C group 6 member A (GPRC6A) [63], zinc transporter member 9 (ZIP9) [64], and transient receptor potential melastatin 8 (TRPM8) [65]. A GPCR that is thought to mediate some of the E2 effects is the orphan G protein–coupled receptor, G protein–coupled ER1 (GPER1, also known as GPR30) [66]. *Gper1* knockout mice have been generated by several groups [67,68]. Little overlap was found to the phenotype observed in ERα or ERβ null mutants, suggesting that

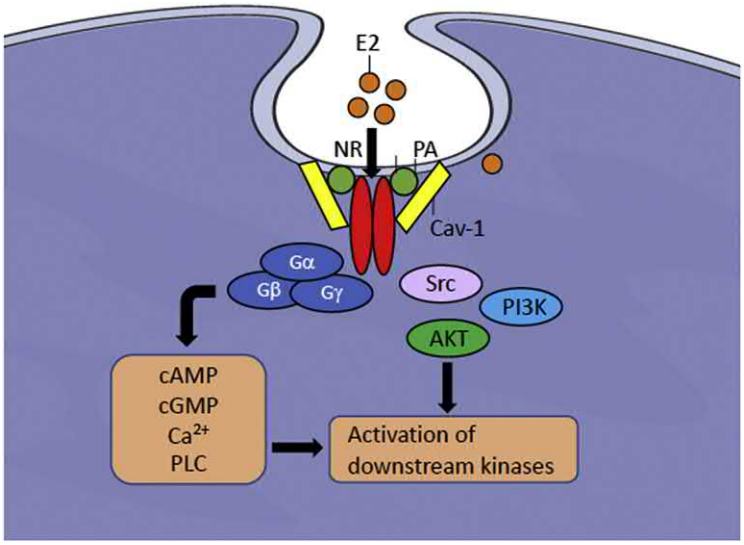

FIGURE 2.6 Nongenomic response of sex steroids is mediated by plasma membrane–localized palmitoylated nuclear receptors. Steroid receptors (NRs) at the plasma membrane are modified through palmitoylation and recruited to caveolae through the interaction with Cav-1. Downstream of this signaling complex are G proteins and various kinases (such as AKT; Src or Pi3K) leading to the production of second messengers (cAMP, cGMP, Ca^{2+}), phospholipase C (PLC), and the activation of various kinase. *Adapted from Sever R, Glass CK. Signaling by nuclear receptors. Cold Spring Harb Perspect Biol 2013;5(3):a016709.*

GPER1 probably only in some cell types mediates some aspects of E2 signal transduction [60]. Interestingly, a cardiomyocyte-specific ablation of *Gper1* revealed alterations in cardiac structure, impaired systolic and diastolic function in both sexes with more profound changes in male mice [69].

Alternatively, nongenomic signaling may involve plasma membrane–localized steroid receptors. Palmitoylation signals are present in both ERs and the AR and plasma membrane localization for all three receptors have been observed (Fig. 2.6). The palmitoylated receptor interacts with caveolin-1 protein (Cav-1) and is recruited into caveolae. Downstream signaling involves the activation of G proteins and downstream second messenger (cAMP, cGMP, Ca^{2+}, and IP3) as well as various kinase cascades (AKT, Src, and PI3 kinase) [60].

In order to distinguish between effects caused by the membrane-localized and the nuclear steroid receptor pools, membrane-only estrogen α receptor (MOER) mice were generated by substituting the gene encoding the full-length ERα receptor with a construct expressing only its E domain. The E domain contains the ligand-binding domain but lacks any DNA-binding activity. These mice retained several rapid responses to steroid signals such as ERK signaling, PI3K–AKT activation, cyclic nucleotide, and calcium flux [70], suggesting that these responses are mediated through the membrane-bound ERα.

To determine the effect of membrane ERα signaling on gene transcription and to distinguish it from nuclear receptor signaling, WT, homozygous MOER and *Esr1* knockout mice were injected with an ERα agonist after being ovariectomized. WT and MOER mice showed a strong transcriptional inhibition of many lipid synthesis–related genes, which therefore only require membrane-localized ERα receptor signaling [71].

Nuclear-only estrogen receptor a (NOER) mice retain nuclear signaling but have lost membrane localization by a knockin of an essential cysteine residue important for palmitoylation. Homozygous NOER females display an array of abnormalities including infertility due to abnormal uterus and ovary formation and aberrant mammary development. Moreover, these mutants display aberrant gene expression during uterine development [72].

Membrane signaling plays a role in mediating the effects of ERβ signaling on cardiac homeostasis. Membrane-localized ERβ signals through PI3K induce the expression of the modulatory calcineurin–interacting protein 1 (MCIP1). MCIP1 binds calcineurin at the catalytic site preventing it from getting activated in response to calcium activation, which also blocks nuclear factor of activated T cells (NFAT) dephosphorylation through calcineurin. AngII stimulates transforming growth factor beta (TGFβ) that stimulates the formation of myofibroblast. Membrane ERβ signaling through AMP-activated protein kinase (AMPK) and protein kinase A (PKA) inhibits transforming growth factor beta (TGFβ) expression in response to AngII stimulation [73]. Additionally, PKA blocks c-Jun kinase activation by TGFβ signaling and, as a result, fibrotic genes are not stimulated [74].

Like the estrogen receptor, also the AR is expressed in many cells of the cardiovascular system including cardiac myocytes [53], endothelial cells [54], and vascular smooth

muscle cells [55]. Testosterone and DHT added to cardiac myocyte cultures are inducing a hypertrophic response including increased protein synthesis and *Nppa* expression [56]. Androgen effects on cardiac myocytes have been studied in mice lacking *AR* [57]. These mice, when infused with AngII, display a reduced hypertrophic response compared to WT mice. However, both left ventricular function and cardiac fibrosis were worsened.

Sex-specific differences in cardiovascular function

Primary and secondary sexual characteristics of males and females are obvious; however, there are also many other differences in physiology, morphology, or behavior and relevant to this book also with regard to cardiac anatomy and physiology. These differences are called sexual dimorphism and describe collectively the differences between male and female of a given species. Darwin has proposed that sexual dimorphism is subject to sexual selection arising from differential mating success [75]. However, there may also be some other selective pressures such as survival or physiological requirements, which are selected for a particular phenotype. Very early on after ECG analysis has been invented, the first differences between the ECG of men and women were described [76]. Thus, as will be outlined throughout this book, women have a longer QT_c than men. Such differences make the female heart susceptible for some specific forms of ECG abnormalities such as ventricular tachycardia or Torsade de Pointes. Apart from QT_c time, there is also a documented sex-dependent difference in the timing, dispersion, and morphology of the T wave [77].

Even in a simple parameter such as heart weight, there is a significant difference between males and females, i.e., even when corrected for body weight, the male heart of many species is hypertrophied relative to the female heart [78]. Clinical observations give support to the existence of sex differences in CVD prevalence and severity. Women exhibit a delay in the development of vascular disease, suggesting that the female sex protects from the development of atherosclerosis. The link between sex and vascular disease susceptibility becomes more evident by the fact that the number of vascular events rise after menopause, which suggests that ovarian hormones may reduce the risk of vascular disease [79,80].

While the incidence of heart failure (HF) is the same between both sexes, women are 65% less likely to develop HF with reduced ejection fraction (HFrEF) (left ventricular ejection fraction (LVEF) $\leq$40%) than men [81]. However, HF with preserved ejection fraction (HFpEF) (LVEF <55%) is twice as common in women than in men [82]. These data suggest that female hearts respond differently to the same pathological stimuli. Support for this notion stems from the observation that in pressure overload due to aortic stenosis or hypertension, the female heart responds with a concentric hypertrophy and an increase in left ventricular wall thickness, while male hearts develop eccentric hypertrophy characterized by a dilatation without an increase in wall thickness [83].

These clinical observations have fostered great interest in understanding the molecular basis of sex-specific differences in CVD, which may also yield novel therapeutic targets. Based on the initial data that females and males show differences in disease progression and that these differences disappear in postmenopausal women, the pathology and morbidity stimulated several studies involving hormone replacement therapy (HRT). These studies, however, gave very conflicting results: the Women Heath Initiative (WHI) and the Heart and Estrogen/Progestin Replacement Study (HERS I and II) demonstrated no obvious benefit of HRT on CVD but actually an increased risk of CVD in postmenopausal women [84–86]. In contrast, some observational studies done earlier found clearly evidence for a positive effect [87]. The discrepancy may be explained by the time when HRT was started as treatment in women below 60 showed a benefit, while this benefit no longer existed in older women (>60) [88]. The timing hypothesis was subsequently specifically addressed in two studies: Kronos Early Estrogen Prevention Study (KEEPS) and the Early versus Late Intervention Trial with Estradiol (ELITE). Both studies came to the same conclusion and demonstrated benefit of HRT when women started the therapy in early menopause [89]. What will be important is to elucidate what causes this timing effect. Possibly this has to do with the expression of the estrogen receptors, which may be downregulated or present only at very low level in postmenopausal women. Indeed, expression of both ERα and ERβ in the heart is modulated by E2 [46].

Animal models to identify sex-specific pathways

Rodents are the preferred model organism in biomedical research and are also extensively utilized in case of sex hormone–related research. As mentioned already, knockout mice harboring null mutations for the three estrogen receptors (*Esr1* [43], *Esr2* [50], and *Gper* [67,68]) and the *AR* [52] have been engineered (Table 2.1). Importantly, conditional alleles for all four receptor genes, which allow to evaluate receptor function in cell type–specific manner, have also been prepared [90–93]. To distinguish between membrane nonnuclear or nuclear effects of steroid receptors, MOER [70] and NOER [72] mutants have been produced for ERα but are not yet available for ERβ. In order to control for hormonal status of the animals, the main glands of

TABLE 2.1 Mouse models to study sex-dependent cardiovascular traits.

Allele	Protein	Function	Purpose	References
Esr1^{-}	Estrogen receptor α (ERα)	Global null mutant	Functions of ERα	[43]
Esr1^{flox}	Estrogen receptor α (ERα)	Conditional allele	Cell type–specific functions of ERα	[90]
Esr1^{MOER}	Estrogen receptor α (ERα)	Membrane-only ERα (*MOER*)	Compartment-specific functions of ERα	[70]
Esr1^{NOER}	Estrogen receptor α (ERα)	Nuclear-only ERα *(NOER)*	Compartment-specific functions of ERα	[72]
Esr2^{-}	Estrogen receptor β (ERβ)	Global null mutant	Functions of ERβ	[50]
Esr2^{flox}	Estrogen receptor β (ERβ)	Conditional allele	Cell type–specific functions of ERβ	[91]
Esr1^{-}/ *Esr2*$^{-}$	Estrogen receptor α/β	Double receptor KO	Functions of ER	[111]
Gper^{-}	G protein–coupled estrogen receptor (GPER)	Global null mutant	Functions of GPER	[67,68]
Gper^{flox}	G protein–coupled estrogen receptor (GPER)	Conditional allele	Cell type–specific functions of GPER	[92]
AR^{-}	Androgen receptor (AR)	Global null mutant	Functions of AR	[52]
AR^{flox}	Androgen receptor (AR)	Conditional allele	Cell type–specific functions of AR	[93]
CYP19a1^{-}	Aromatase	Global null mutant	Function of aromatase Local steroid production	[41]
FCG	Four core genotypes	Transgenic mouse line	Sex chromosome effects	[104]

production (ovar and testes) are often surgically removed (ovarioectomy and orchiectomy) and hormones are substituted by injection, pump, or patch. However, it is important to realize that an ovarioectomy would not eliminate the local tissue production, which may be sufficient to maintain gene expression of some steroid-regulated genes. At present, investigation of a cardiac-specific ablation of *CYP19a1* has not been done so far.

In order to investigate the underlying molecular mechanism of sex differences in CVD, the use of exogenous E2 in ovariectomized female mice is common practice to demonstrate an effect of female sex steroids. In this regard, it is important to be aware of differences in estrous cycle between mice and men. Mice have an estrous cycle of 4–5 days which is significantly shorter than in men (approximately 28 days). Moreover, mice do not develop menopause.

To verify the roles of ERα and ERβ in mediating the beneficial effects of E2 can be studied with the help of *Esr1* and *Esr2* null mutants. Babiker et al. reported that addition of E2 in case of ovariectomized *Esr1* null mutants resulted in a reduced ventricular weight comparable to WT littermates [94]. The same effect was not obtained in case of the *Esr2* null mutant, suggesting that ERβ mediates this effect. A similar conclusion was drawn from a study of transverse aortic constriction of male and female WT and *Esr1* and *Esr2* null mutants [95]. The hypertrophic response of WT males was stronger than in females. *Esr1* null mutant females responded in the same way as WT females, while *Esr2* null mutants developed more cardiac hypertrophy. Interestingly, male *Esr2* null mutants did not differ from WT males, suggesting that the protective effect of ERβ is relevant for females but not for males. In a study utilizing voluntary exercise–induced physiological hypertrophy, females developed a higher heart mass than their male counterparts. Significantly, these differences were lost in case of the *Esr2* null mutants. WT females displayed an increased phosphorylation level of several kinases (AKT, ERK1/2, p38-MAPK) and increased level of regulators of mitochondrial function [96]. While ERβ is important for the myocardium, there is also evidence that the ERα mediates protective effects of E2 against vascular injury [97]. The importance of both receptor types has also been studied in a cardiomyocyte-specific manner using floxed alleles for *Esr1* and *Esr2* [98]. Structural defects and an alteration of more than 200 genes belonging to different pathways are affected by the cardiac-specific ablation of *Esr1*. In case of cardiac-specific ablation of *Esr2*, a DCM-

like phenotype and impaired calcium homeostasis have been described [99]. Cardiac-specific loss of *Gper1* causes ventricular dysfunction and remodeling [92]. These data therefore suggest that the three estrogen receptor types have cell autonomous functions in cardiac myocytes.

The zebrafish is a novel model organism to study cardiovascular development and is also emerging as a useful adjunct model to elucidate physiological and pathophysiological processes in the heart and other organs. E2 is able to raise the heart rate in zebrafish embryos. Both pharmacology and genetic approaches using homozygous null mutants for all four ER receptor genes present in the zebrafish genome *(esr1*, *esr2a*, *esr2b*, and *gper)* provided strong evidence that this physiological response is selectively mediated by Gper-dependent signaling [100]. Expression studies suggest that this effect is noncell autonomous as Gper in the zebrafish embryo is exclusively expressed in different parts of the brain but absent from the heart. Basal heart rate is not dependent on *Gper* in adult mice, suggesting that either this phenotype observed in zebrafish is unique to this species or unique to the embryonic heart [101].

Sex differences in the susceptibility to ischemia/reperfusion (I/R) injury have been demonstrated in humans. Premenopausal women have a lower risk of ischemic heart disease than age-matched men, whereas after menopause the risk is similar or even higher in women [80]. It is believed that the lower risk to develop coronary artery disease in premenopausal women is related to female sex hormones. The protective role of E2 has been demonstrated in the context of myocardial I/R injury in numerous experimental models including estrogen receptor (ER) knockout animals [102]. In contrast to these findings, however, HRT was found to be ineffective to lower the risk of ischemic heart disease in postmenopausal women. Therefore, the focus shifted toward the difference in the number of X chromosomes in both sexes. In order to be able to uncouple chromosomal sex (X/X vs. XY) from gonadal sex (ovaries and testes) and the production of the respective sex hormones, the four core genotypes (FCGs) mouse models are utilized [103,104]. These animals have moved the *Sry* gene from the Y chromosome to an autosome. Therefore, homogametic (X/X) or heterogametic (X/Y) gonadal females and males can be produced and gonadal and chromosomal sex can be uncoupled and independently studied. The FCG mice were used to test whether the number of X chromosomes influences myocardial protection for ischemia reperfusion [105]. Surprisingly, and counterintuitive, animals with two X chromosomes had larger infarct size than animals with only one X chromosome. So why the number of X chromosomes matter? The authors hypothesized that genes that escape XCI might cause the effects of X-chromosome dose. Since those genes that do escape XCI are all known, the authors compared the expression levels of these genes in XX and XY hearts. Fours genes were found to be expressed at higher levels in XX hearts, and two of these are histone demethylases acting as chromatin-modifying genes and having widespread effects on gene expression. These data strongly demonstrate that also chromosomal effects need to be considered to explain sex-specific differences in cardiac disease phenotypes.

Another example of a chromosomal effect on cardiac phenotype development has also been revealed using the FCG mice. An extreme sensitivity of XY females for AngII-induced abdominal aortic aneurysms was recently established [106]. It was already known for some time that patients with a Turner syndrome (monosomy, X0) have an increased (12 times) higher risk of aortic dissection [107].

XY female mice displayed an increased expression of inflammation markers and metalloproteases in the aorta. These findings clearly establish that sex is determined at several levels and is not simply controlled only at the sex steroid level. Far more research is required into the complex network of molecular elements that play a role in sex determination and differentiation, many of which have an unexpectedly strong influence on myocardial structure and function in the healthy and diseased heart.

However, to gain further insight into sex-specific genetic traits, it is important that investigators studying CVD or cardiac gene function will analyze not only male but also female mice and test whether there is evidence for a sex-specific trait. Traditionally, many genetic studies are investigating the phenotype of mutants using males. This is usually based on the fact that females will be utilized as breeders and the female estrous cycle is considered to cause additional complexity of phenotype analysis. However, a recent analysis of molecular traits revealed no higher variability in female versus male mice [108]. The National Institute of Health announced recently that sex must be considered as a biological variable in all NIH-funded preclinical research and mandated the inclusion of women in clinical research [109]. Similar funding conditions will also be required worldwide to promote research to unravel the biological basis of sex as a determinant of myocardial structure and function in health and disease.

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Part II

Cellular and tissue electrophysiology

Chapter 3

Effects of sex hormones on cardiac ion channels involved in ventricular repolarization

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Ionic basis of ventricular action potentials

There are numerous review articles written about the diversity of cardiac ion channels and their regionally defined expression patterns that produce distinct action potential (AP) characteristics in different regions of the heart [1,2]. Rather than revisiting this topic in detail, a simplified scheme of ventricular AP and its relation to ECG is presented here to set stage for subsequent sex difference comparisons.

The top panel of Fig. 3.1 shows a schematic diagram of a ventricular AP. The upstroke of the AP (phase 0) is mediated by the large and rapid Na^+ influx through $Na_V1.5$ channels. With membrane depolarization, $Na_V1.5$ channels quickly undergo voltage-dependent inactivation, while $Ca_V1.2$ (L-type Ca^{2+}) channels are activated. The fast Ca^{2+} transient through $Ca_V1.2$ channels drives excitation–contraction coupling, while the sustained component through these channels contributes to generate the plateau potential. Phase 1 repolarization, seen as a notch, is mainly caused by $Na_V1.5$ channel inactivation and activation of the transient outward K^+ currents I_{to} (mediated by $K_V4.2$, $K_V4.3$, and $K_V1.4$ channels). Increase in intracellular Ca^{2+} leads to Ca^{2+} extrusion by Na^+-Ca^{2+} exchanger (NCX1), which removes 1 Ca^{2+} out of the cell while bringing 3 Na^+ into the cell. When operating in this forward mode, the NCX current (I_{NCX}) is depolarizing, hence also contributes to AP duration (APD). The plateau phase or phase 2 of the ventricular AP thus reflects continued Ca^{2+} and Na^+ influxes through $Ca_V1.2$ channels, some $Na_V1.5$ channels that enter distinct gating modes to give rise to the late Na^+ current (I_{NaL}), and NCX1 that together balance the effect of K^+ efflux through K^+ channels. The decay of Ca^{2+} current, the increase in the delayed rectifier K^+ currents I_{Ks} (mediated by $K_V7.1$/minK channels) and I_{Kr} (mediated by hERG or $K_V11.1$ channels), and the late activation of the inward rectifier K^+ current I_{K1} (mediated by homomeric or heteromeric assembly of $K_{ir}2.1$, $K_{ir}2.2$, and $K_{ir}2.3$ subunits) are responsible for phase 3 repolarization. Phase 4 marks the return to the resting membrane potential (RMP), and is largely mediated by I_{K1}. As Fig. 3.1 shows, ventricular APD is determined by the integrated activities of inwardly depolarizing and outwardly repolarizing ionic currents that underlie phases 2 and 3 of the AP.

The bottom panel of Fig. 3.1 shows the cardiac waveform morphology on the ECG during ventricular depolarization (the QRS-complex) and repolarization (from the J-point to the end of the T-wave). This ECG signal reflects the vectorial sum of different ionic currents in all the cardiac myocytes. The QT-interval, measured from the beginning of the QRS-complex to the end of the T-wave, represents the duration of ventricular myocardium activation and recovery, hence is an indirect measurement of the ventricular APD.

Sex differences in ventricular repolarization

Women have a higher resting heart rate than men [3,4], yet have longer QT and rate-corrected QT (QT_C) intervals [5–13]. The rate-dependent adaptation in QT interval is steeper in women than in men [8,14], resulting in a QT difference that is accentuated at long cycle lengths and diminished at short cycle lengths [8]. The difference in QT_C

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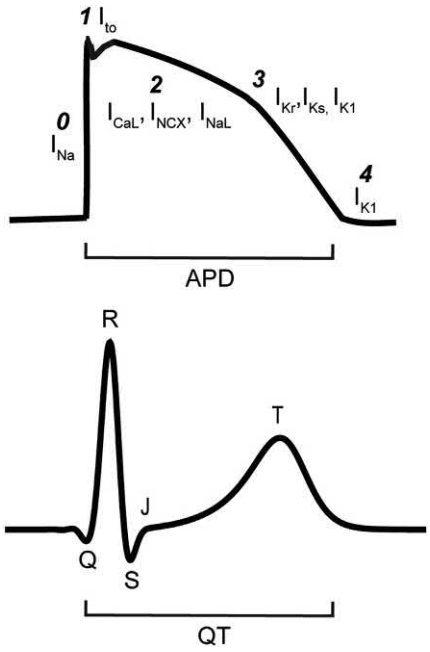

FIGURE 3.1 Relationship between the ventricular action potential (AP) and ECG intervals. *Top panel*, a schematic diagram of a human ventricular AP with 4 phases labeled. I_{Na}, Na^+ current mediated by $Na_V1.5$ channels; I_{CaL}, L-type Ca^{2+} current mediated by $Ca_V1.2$ channels; I_{NCX}, Na^+–Ca^{2+} exchanger current generated by NCX1; I_{NaL}, late Na^+ current mediated by $Na_V1.5$ channels; I_{Kr}, rapidly activating delayed rectifier current mediated by hERG or $K_V11.1$ channels; I_{Ks}, slowly activating delayed rectifier current mediated by $K_V7.1$/minK channels; I_{K1}, inward rectifier current mediated by homomeric or heteromeric assembly of $K_{ir}2.1$, $K_{ir}2.2$, and $K_{ir}2.3$ subunits. *Bottom panel*. An ECG. P wave is not shown.

also persists after double autonomic blockade [15,16], suggesting that it involves cellular processes underlying ventricular repolarization that are *intrinsic to the heart and frequency-dependent*. Voltage-dependent cardiac ion channels in ventricular myocytes fulfill these two requirements, and differences in their activity levels in men and women are thought to contribute to sex differences in ventricular repolarization.

Analyses of ECG parameters within the QT interval show that men are more likely to exhibit J-point elevation [10,17], have steeper ST-slope [10,17], and shorter J-T_{peak} interval [6,12]. As these variables are thought to reflect the early phase of repolarization in ventricular myocytes, sex difference in the QT_C interval has been suggested to involve shorter early [10,12,17] but not late ventricular repolarization in men compared to women [12,17]. Analysis of the T-wave shows that men have steeper slopes of both the ascending and descending limbs and larger amplitude than women [18]. As the T-wave reflects aggregated repolarizing activities in ventricular myocytes as they course through phase 3 of the AP, sex differences in the T-wave morphology suggest that men and women differ in both the earlier and later portions of phase 3 of the AP as well as AP dispersion across the myocardium. Finally, T_{peak}–T_{end} interval is significantly longer in men than in women over a range of heart rates [19]. Because this parameter has been proposed to reflect heterogeneity of APD within the ventricular wall, intraventricular repolarization gradient, set forth by different cell properties within the myocardial layers of the ventricular wall, also likely exhibits sex differences. Indeed, results from humans [20] and animals [21–23] that demonstrate regional differences in ion channel expression or activities are consistent with this interpretation. Altogether, sex differences in ventricular repolarization parameters are associated with findings that women are generally at higher risk of long QT-associated arrhythmias such as Torsade de Pointes [24–28]. Men on the other hand are more likely to present with early repolarization [29,30], idiopathic ventricular fibrillation [31], and Brugada syndrome [32].

One mechanism that can lead to a sex difference in ventricular repolarization is differences in the activities of various cardiac ion channels (and electrogenic proteins) that underlie phases 2 and 3 of the AP between men and women. Consistent with this hypothesis, different expression levels of ion channel–related genes and proteins have been reported in ventricular tissues of men and women [20,33]. Female ventricles show reduced expression of many K^+ channel subunits including hERG, minK (β subunit of $K_V7.1$), $K_{ir}2.3$, $K_V1.4$, KChiP2 (auxiliary subunit of $K_V4.2$ and $K_V4.3$ that also regulates $Na_V1.5$ and $Ca_V1.2$ channels [34]), $K_{ir}6.2$ (ATP-dependent inward rectifier), and SUR2 (regulator of $K_{ir}6.2$) relative to male ventricles (Fig. 3.2). In contrast, no sex difference was found in the level of $Na_V1.5$ transcript. Protein levels for hERG, minK, $K_V1.4$, KChiP2, and $Na_V1.5$, paralleled transcript patterns, suggesting that women have a reduced repolarization drive relative to men. A subsequent study found that sex difference in ventricular ion channel expression is complex, exhibiting region- and age-dependence [20]. Analysis of select ion channel and Ca^{2+} handling proteins showed that the levels of $Ca_V1.2$, NCX1, and SERCA2A (a Ca^{2+} ATPase which sequesters Ca^{2+} into the sarcoplasmic reticulum or SR) were higher at the base than apex of the endocardium for younger women (17–49 years), but not men (32–58 years) or older women (51–68 years) (Fig. 3.3). Expression pattern of hERG was the opposite in younger women, tending to be higher at the apex than base. Such apex-base expression pattern predicts that in young women, APD is longer in myocytes from the base than apex. Data from female rabbit hearts support this idea, and further show that the resulting intraventricular repolarizing gradient promotes proarrhythmia in response to I_{Kr} inhibition in female hearts relative to male hearts [22,23]. Unexpectedly, the reverse pattern for hERG expression was found in men and older women, with hERG tending to be more abundant at the base than apex. No

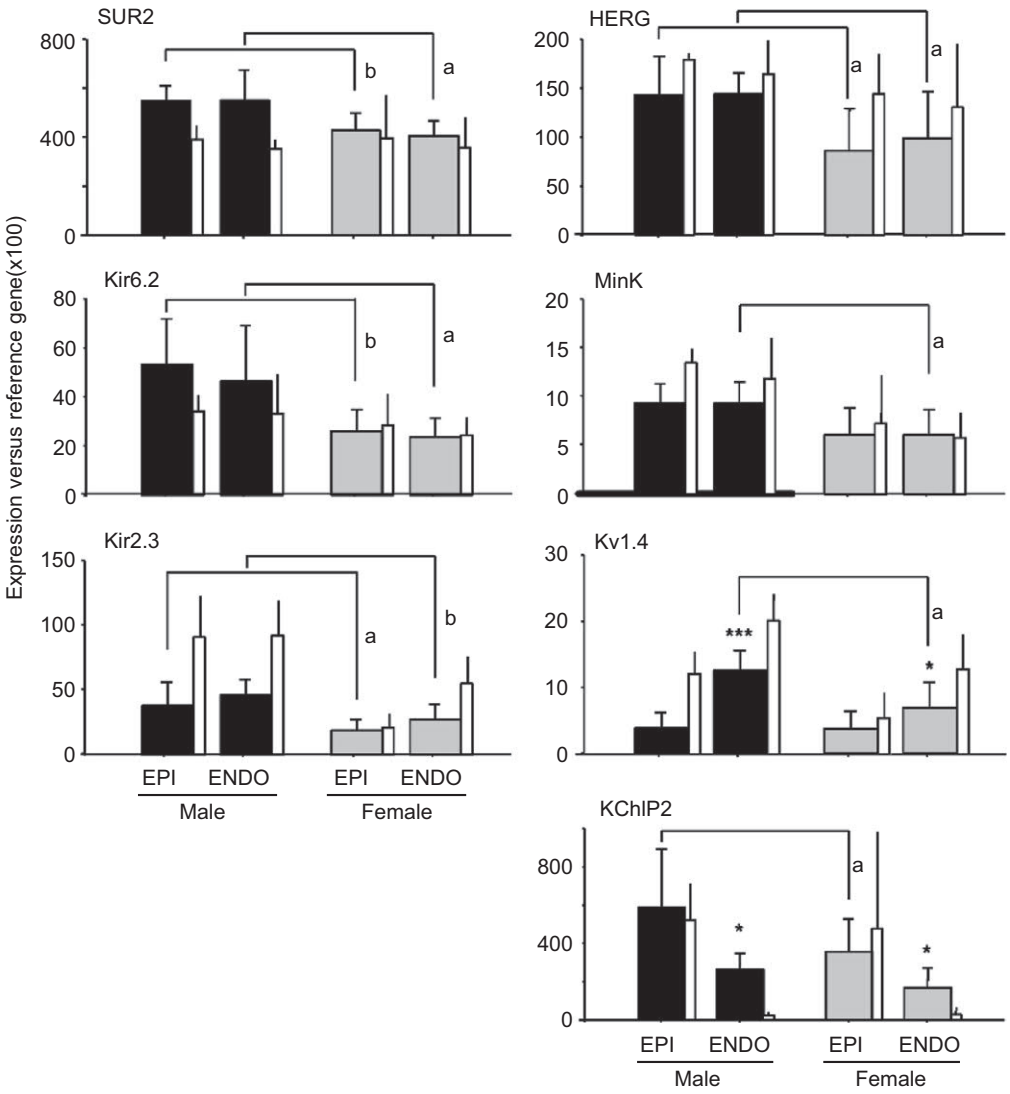

FIGURE 3.2 Expression profile of K^+ channel–related genes in human male and female ventricles. *Thick bars* show transcript expression in the right ventricles. Left ventricle data are represented by *narrow bars*. Results are shown as mean ± SD from 7 donors for each sex. Epi = epicardium; endo = endocardium. *$P < .05$, ***$P < .001$ versus epicardium; a: $P < .05$; b: $P < .01$ versus women. Left ventricle statistics are as follows: epicardium versus endocardium: male, $K_V1.4$, $P < .01$; KChIP2, $P < .001$. Female, $K_V1.4$, $P < .05$; $K_{ir}2.3$, $P < .01$, KChIP2, $P < .01$. Male epicardium versus female: Kir2.3, $P < .001$; hERG, $P < .05$; minK, $P < .01$; KV1.4, $P < .01$. Male endocardium versus female: Kir2.3, $P < .05$; minK, $P < .01$; $K_V1.4$, $P < .05$. *This figure was modified and reprinted with permission from Elsevier from Gaborit N, Varro A, Le Bouter S, Szuts V, Escande D, Nattel S, Demolombe S. Gender-related differences in ion-channel and transporter subunit expression in non-diseased human hearts. J Mol Cell Cardiol 2010; 49:639–46. Copyright 2010.*

regional difference was found in $Na_V1.5$ expression, consistent with Gaborit et al. [33]. Together, these two studies demonstrate that human ventricles exhibit sex difference in the expression of many cardiac ion channels that contribute to APD. *Accordingly, drugs that act on these ion channels are expected to produce different electrophysiological effects in men and women, creating different cellular conditions that differ in susceptibility to ventricular arrhythmias*. Note that one study that used ventricular tissues from older donors (~50 years) did not detect any sex difference among transcripts of 89 ion channel subunits, Ca^{2+} handling proteins, and transcription factors [35]. Based on the results from Papp et al. [20], a possible explanation for the lack of sex difference is the donor age and/or regional variations in tissue selection.

Involvement of sex hormones in ventricular repolarization

Sex difference in the QT_C interval is absent at birth [36] and appears around the time of puberty [10,37]. After puberty, boys exhibit QT_C shortening, while girls show no

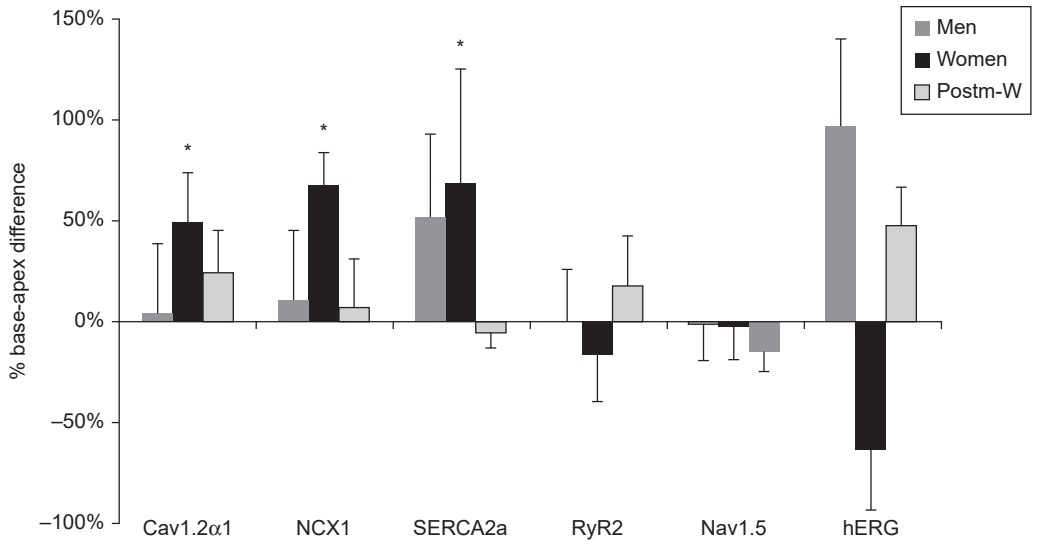

FIGURE 3.3 Comparison of protein expression between the base and apex of the left ventricular epicardium in humans. The histogram shows normalized protein band intensities expressed as base−apex percent differences derived from an analysis of tissue samples from 6 men, 11 women, and 6 menopausal women. *This figure was adapted from Papp R, Bett GCL, Lis A, Rasmusson RL, Baczko I, Varro A, Salama G. Genomic upregulation of cardiac Cav1.2alpha and NCX1 by estrogen in women. Biol Sex Differ 2017;8:26, which is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/) that permits unrestricted use in any medium.*

change or slight QT_C lengthening. With age, the QT_C interval continues to increase, at a faster rate in men than in women [12,38]. As a result, QT_C difference is attenuated in the elderly (>50 years) [10,11,37]. Consistent with these results, Ambrosi et al. reported no difference in ion channel expression pattern between ventricular tissues of older men and women [35]. Since QT_C difference emerges with reproductive maturity and then disappears following reproductive senescence—two life stages brought about by changes in sex hormone levels, it seems plausible that sex hormones contribute to sex difference in ventricular repolarization. Indeed, one study found that in heart transplant patients, donor sex has little influence on the QT_C interval. Instead, the QT_C interval tends to be longer in female heart transplant recipients compared to male recipients regardless of donor sex, suggesting that factors intrinsic to the recipients, including circulating sex hormone levels, play a more deciding role in regulating ventricular repolarization [13].

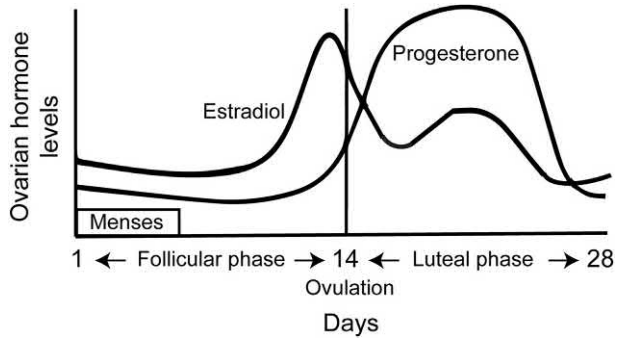

FIGURE 3.4 Changes in estradiol (E_2) and progesterone (P_4) levels over a single menstrual cycle in women.

There is strong evidence from human studies suggesting that testosterone (T) regulates ventricular repolarization. In older men (≥55 years), there was an inverse association between the circulating T level and the QT_C interval [39,40]. In patients with endocrine disorder, male patients who experienced chronic androgen deprivation due to castration had slower and longer ventricular repolarization than intact men, while female patients with a virilization syndrome and experienced higher level of circulating T showed shorter and faster repolarization than castrated men and control women [41]. Thus, T seems to shorten the QT_C interval in both men and women. In contrast to T, the roles of ovarian hormones 17 β-estradiol (E_2) and progesterone (P_4) are equivocal due to conflicting reports. During the reproductive years, circulating levels of E_2 and P_4 fluctuate during the menstrual cycle, with the lowest E_2 level at the beginning of menses, which then slowly rises in the follicular phase to reach the preovulatory peak in the late follicular phase (Fig. 3.4). Thereafter, E_2 level declines and reaches a second peak during the luteal phase. P_4 level is the lowest during menses and the follicular phase, and steadily increases to become the dominant hormone during the luteal phase. To address the involvement of ovarian hormones in ventricular repolarization, several studies have compared the QT_C interval across the menstrual cycle in women. One study reported that QT across all RR intervals or heart rates was significantly shorter in the luteal than the early follicular phase prior to the E_2 surge [42]. Because E_2

level measured in this study was similar between the luteal and the early follicular phases (on average 253.3 vs. 279.0 pM, respectively), while P_4 level was much higher in the luteal phase (on average 16.7 vs. 1.6 nM in the early follicular phase) as was the noradrenaline level, the shorter QT interval seen at the luteal phase was interpreted to reflect either P_4's action on ventricular repolarization or sympathetic tone difference. Another study compared the QT intervals across a range of heart rates at menstrual cycle phases that differed in E_2 but not P_4 level [43]. In this study, E_2 level measured during menses was 105 ± 34 pM, and during the preovulatory surge was 750 ± 277 pM. P_4 levels measured during these two phases were 3.2 ± 4.1 and 2.9 ± 2.0 nM, respectively. No significant difference in the QT interval was observed, suggesting that E_2 fluctuation within the measured concentrations does not affect ventricular repolarization. Three additional studies compared QT_C interval in women at three different menstrual cycle phases and found no difference under baseline condition [9,15,44]. However, two of these studies found that differences emerged following double autonomic blockade [15,44]. In one of the studies, the QT_C interval was shorter during the luteal phase than the menstrual or the late follicular phase, suggesting that P_4 caused QT_C shortening [15]. In the other study, QT_C interval was longer during the follicular phase relative to the luteal or menstrual phase, suggesting that E_2 causes QT_C prolongation [44]. In spite of having no QT_C difference across the menstrual cycle under baseline condition, Rodriguez et al. found that maximum QT_C increase following ibutilide infusion was greater for women during menses and ovulatory phase compared with women during the luteal phase and men [9]. Given that ibutilide inhibits I_{Kr} to prolong ventricular repolarization, it seems plausible that *activities of various cardiac ion channels that contribute to APD could vary across the menstrual cycle, thereby giving rise to different extent of APD prolongation postdrug even though predrug QT_C measurements did not detect a difference*. That activities of various ventricular ion channels could be altered without producing overt changes in APD or ventricular repolarization has been demonstrated in modeling studies [45] as well as animal experiments [21]. Using a human ventricular myocyte AP model, Dutta et al. identified scaling factors for five ionic conductances corresponding to I_{Kr}, I_{Ks}, I_{K1}, I_{CaL}, and I_{NaL} that did not change APD under the control condition but altered APD when simulating drug block of different ion channels. In a dog study, $K_V4.3$ and $K_{ir}2.1$ protein levels (mediate I_{to} and I_{K1}, respectively) were higher in the male than the female ventricles even though a sex difference in QT or QT_C was not detected [21]. Rodriquez et al. also showed that in women, serum P_4 and P_4-to-E_2 ratio, but not E_2 or T level, were inversely correlated with ibutilide-induced QT_C prolongation, suggesting that P_4 is protective against ibutilide-induced QT_C prolongation [9]. In support of this idea, another study found that P_4 treatment during menses (when serum E_2 and P_4 are expected to be at the lowest) was associated with QT_C shortening and reduces QT_C prolongation in response to ibutilide in comparison with placebo-treated subjects [46].

Studies that compared the effects of unopposed estrogen replacement therapy (ERT) and progestin-estrogen replacement therapy (PERT) on the QT_C interval have offered some clarity regarding the roles of E_2 and P_4 on ventricular repolarization. In postmenopausal women, unopposed ERT was associated with QT_C prolongation [47–50] and increased QT dispersion [50]. In contrast, PERT was associated with reduced QT dispersion [47], reduced QT_C interval [49,50], or no QT_C difference compared with the never-users [48]. These results clearly demonstrate that E_2 prolongs the QT_C interval, whereas P_4 counters E_2's effects. In contrast, several studies reported no effect of hormone replacement therapies on the QT_C interval [51–54]. In two of these studies, one had statistical power to detect large QT_C interval difference (80 ms) only based on the sample size [54], while the other did not specify the type of hormone replacement therapy that the participants used in the study [53,54]. For the other two studies, De Leo et al. found that premenopausal women who underwent oophorectomy and experienced ovarian hormone loss for 20–25 days had an increase in the T-wave duration, a decrease in its amplitude, and a decrease in ST depression [51]. These changes implicate changes in phase 3 AP repolarization as well as AP dispersion and were reversed by subsequent E_2 treatment for 30–35 days, suggesting that they were induced by E_2 loss. Saba et al. described prolonged QT dispersion in postmenopausal women who were not using hormone replacement therapy compared with those who were using hormone replacement therapy and premenopausal women, suggesting that uncompensated ovarian hormone loss had an impact on the heterogeneity in ventricular recovery time [53].

Altogether, the human studies presented above have provided reasonable evidence that ovarian hormones, like androgens, regulate ventricular repolarization. In general, E_2 is associated with prolongation of ventricular repolarization, whereas P_4 counters E_2's effect and is generally associated with shortening of ventricular repolarization. An exception to this scheme was reported in a recent study, which showed that supraphysiological E_2 level was associated with reduced QT_C interval [55]. This study evaluated the QT_C intervals in women before, during and after pregnancy, and in women during clomiphene stimulation for infertility. Clomiphene treatment produced supraphysiological E_2 increase, from an average of 374.5 ± 235.0 pM under baseline condition to 4993.0 ± 1424.5 pM under stimulation, without major changes in P_4 level (2.5 ± 0.3 vs. 9.5 ± 5.1 nM,

respectively). High E_2 levels, but not P_4 level or E_2/P_4 ratio, inversely correlated with QT_C interval. Additional studies are necessary to confirm these results and to address the underlying mechanisms in ventricular myocytes.

Chronic effects of sex hormones on cardiac ion channels, ventricular repolarization, and arrhythmia propensity

The classic mechanism of sex hormone regulation is genomic control of target gene expression via binding of the hormone−nuclear receptors complex to the genomic consensus sequence of target genes to regulate transcription. Receptors for androgens and ovarian hormones have been detected in cardiac tissues of many species, including humans (for androgens [56−59]; for estrogen [59−62]; for progesterone [63−65]). The presence of sex hormone receptors in cardiac tissues has provided a rationale for investigating genomic regulation of ventricular ion channels by sex hormones as well as nongenomic yet long-lasting effects of sex hormones on ventricular ion channel activities. Data from human myocytes are rather limited. Animal models that exhibit similar sex differences as humans have been widely used, since these allow for easy manipulation of sex hormones through gonadectomy and subsequent replacement. The animal studies referenced below used rabbits, guinea pigs, and dogs—larger species that exhibit ventricular AP characteristics and ion channel profiles more similar to those found in humans. Results from rats and mice have also provided important insights. They are not highlighted here due to the species' much abbreviated ventricular APs without a plateau phase and the lack of delayed rectifying K^+ currents I_{Kr} and I_{Ks} that are important for ventricular repolarization in humans.

In human-induced pluripotent stem cell−derived cardiac myocytes, chronic exposure to E_2 (1 nM) for 1−2 days increased the current densities and mRNA levels for $Ca_V1.2$ and NCX1 in cells derived from the female but not male donor, demonstrating sex-specific genomic effects of E_2 that occur in female cells only [20]. The changes in current densities were detected in the absence of E_2, thereby excluding acute ion channel modulation by E_2 as possible mechanisms. As Fig. 3.1 illustrates, inward currents mediated by $Ca_V1.2$ channels (I_{CaL}) and NCX1 (I_{NCX}) contribute to APD in ventricular myocytes. Increases in these currents in female cells are expected to prolong APD if not balanced by concomitant increases in outward currents, suggesting that they could contribute to the prolonged ventricular repolarization in female hearts. In HEK cells overexpressing hERG channels and estrogen receptor α (ERα), exposure to E_2 (60 nM) for 48 h led to an increase in hERG current [55]. No change was detected in the hERG mRNA level. Instead, E_2 activated ERα, leading to increased hERG protein trafficking to the cell membrane. Whether this mechanism also occurs in ventricular myocytes or not is currently unclear. Nonetheless, these two studies clearly demonstrate that chronic exposure to E_2 altered activities of three ion channel−related proteins involved in ventricular repolarization.

Rabbits are often used to explore sex differences in ventricular repolarization mechanisms. Similar to humans, female and male rabbit hearts show rate-dependent differences in the QT interval [66−69] and susceptibility to drug-induced ventricular arrhythmias [22]. Densities of I_{Kr} [67], I_{K1} [67], and I_{Ks} [69] were found to be smaller in the female than male ventricular myocytes [67], consistent with the reduced expression levels of hERG, $K_{ir}2.3$, and minK in the ventricles of women [33]. Sex and regional differences have also been described for the densities of I_{CaL} [22,70] and I_{NCX} [23] in rabbit ventricles, consistent with human studies [20]. I_{CaL} [22] and I_{NCX} [23] from the left epicardial ventricular myocytes from the base of the female heart were larger than those from the apex and from the male heart (both apex and base), demonstrating an apex-base gradient in the females. These differences were mediated by elevated levels of $Ca_V1.2$ and NCX1 proteins at the base—a regional difference also found in the ventricular tissues of women but not men [20]. The increased densities of I_{CaL} and I_{NCX} were associated with increased propensity to develop early afterdepolarizations (EADs)—cellular changes thought to initiate Torsade de Pointes [22,23]—and Torsade de Pointes [22] in the females in response to I_{Kr} inhibition (Fig. 3.5). Recordings from rabbit base myocytes cultured in hormone-free media from 1 to 3 days following extraction showed gradual loss of I_{NCX}, while those treated with E_2 for 24 h showed upregulation of NCX1 and I_{NCX}, but only in the base and not apex myocytes. These results demonstrate two sex- and region-specific genomic effects of E_2 on ion channel−related proteins that are associated with proarrhythmia risk in the female hearts.

In addition to the apex-base gradient, I_{CaL} also exhibits transmural gradient in a sex-specific manner [70]. In intact female but not male rabbits, the density of I_{CaL} was larger in the epicardial ventricular myocytes than endocardial myocytes in the papillary muscles, demonstrating a transmural gradient in the females. Ovarian hormone loss for 2 weeks following ovariectomy (OVX) abolished I_{CaL} transmural gradient, whereas 5-α dihydrotestosterone (DHT) or E_2 treatment for 4−5 weeks restored it through a hyperpolarizing shift in the voltage dependence in the channel activation in epicardial cells. DHT is a T derivative often used in animal studies instead of T because it does not get metabolized to E_2 by cytochrome P450 aromatase. Comparing with DHT, E_2 had an additional effect on $Ca_V1.2$ channels: it also increased epicardial whole cell

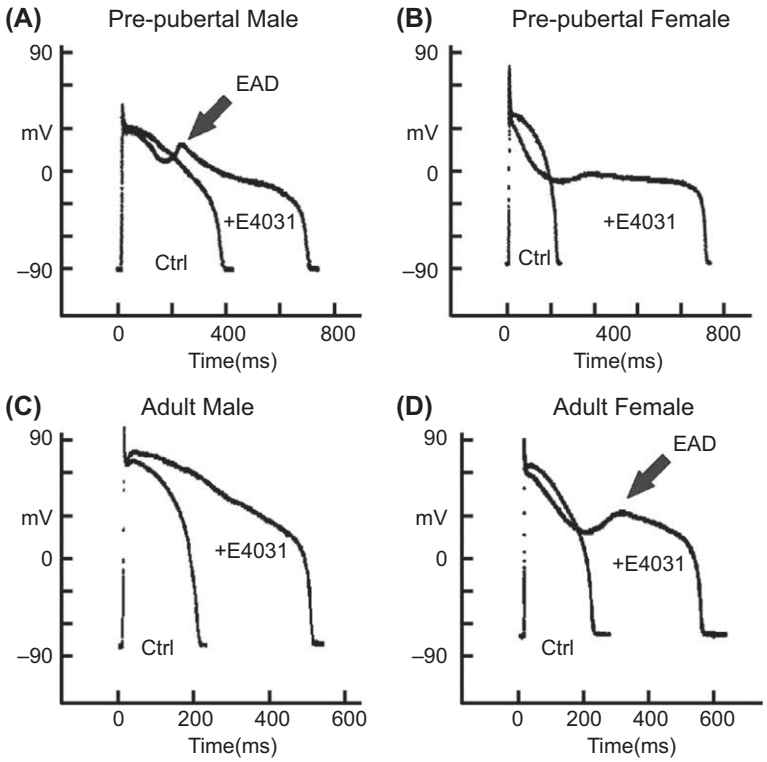

FIGURE 3.5 Early afterdepolarization (EAD) susceptibility in isolated ventricular myocytes from the base of the heart. In myocytes from prepubertal hearts, EADs occurred spontaneously in male (A) (n = 4/4; H = 3) but not in female (B) (n = 0/4; H = 3) ventricular cells. In myocytes isolated from adult hearts, there was a reversal of sex differences; EADs occurred in female (D) (n = 5/6; H = 4) but not in male (n = 0/6; H = 4) myocytes. Note that treatment with E4031 elicited a marked depolarization or EAD (marked by arrows) in adult female and prepubertal male myocytes compared with their adult male and prepubertal female counterpart. Fisher's exact test rejects the null hypothesis of equal probability of EADs between male and female myocytes with $P < .02$, such that statistical significance is reached to predict that EADs are more likely to occur with prepubertal male than female myocytes and more likely to occur with adult female compared with male myocytes. *This figure is adapted with permission from Wolters Kluwer Health, Inc.: Sims C, Reisenweber S, Viswanathan PC, Choi BR, Walker WH, Salama G. Sex, age, and regional differences in L-type calcium current are important determinants of arrhythmia phenotype in rabbit hearts with drug-induced long QT type 2. Circul Res 2008;102(9):e86–100 (https://www.ahajournals.org/doi/10.1161/circresaha.108.173740).*

Ca^{2+} channel conductance. No manipulation in male rabbits, through orchidectomy (ORCH) or subsequent hormone treatment (DHT or E_2), affected $Ca_V1.2$ channel properties in epicardial or endocardial cells. Thus, this study demonstrates that DHT treatment, like E_2 treatment shown by Sims et al. [22], also upregulates I_{CaL} (albeit via different mechanisms) but only in female cells and in a region-specific manner.

Dogs also exhibit similar sex difference in the QT interval as humans [71] (but also see Fulop et al. which showed no difference [21]). Using intact male and female dogs, Xiao et al. found a rather complex set of sex differences in the transmural gradient for APD and three of its underlying currents—I_{to}, I_{Ks}, and I_{CaL} [71]. Ventricular myocytes from epicardium and endocardium showed no sex difference in APD. However, in midmyocardium, APD was significantly larger in female cells than male cells, resulting in a large transmural APD heterogeneity in females. There was no sex difference in I_{Kr} or I_{K1} density across the three myocardial layers, and no sex difference was found in I_{to} density in epicardium and midmyocardium. In endocardium, however, female cells had smaller I_{to} density than male cells. For I_{Ks}, female cells in epicardium and endocardium showed significantly larger current densities relative to male cells, but there was no sex difference in midmyocardium for I_{Ks}. Finally, female cells had larger I_{CaL} densities across all three myocardial layers than male cells. Sex-based transmural differences in I_{to}, I_{Ks}, and I_{CaL} as described in this study may contribute to sex differences in transmural cardiac repolarization.

In addition to $Ca_V1.2$ [22,70], NCX1 [23], and hERG [55], several other ventricular ion channels or ionic currents have also been found to respond to chronic sex hormone manipulations. Androgen loss for 8 weeks following ORCH in male rabbits is associated with a reduction in I_{Ks} density in ventricular myocytes, whereas ovarian hormone loss following OVX is associated with an increase in I_{Ks} density [69]. In DHT-treated ORCH male rabbits (treatment

duration was 10–14 days), I_{K1} and I_{Kr} were significantly increased [68]. DHT treatment did not affect the hERG mRNA level, but rather caused a hyperpolarizing shift in the voltage dependence of current activation, suggesting that DHT's action on I_{Kr} was mediated by post-transcriptional and/or posttranslational modifications. Treatment with E_2 or DHT for 20 days in OVX female rabbits was associated with reduced levels of $K_V1.5$ and minK transcripts, whereas hERG transcript level was unaffected [66]. $K_V1.5$ underlies I_{Kur}, the ultrarapidly activating delayed rectifier important for atrial repolarization. Although $K_V1.5$ proteins are present in ventricular myocytes [72], their function in these cells has not been demonstrated. MinK is the β subunit of $K_V7.1$/minK channel that mediates I_{Ks}, and its reduction is expected to reduce I_{Ks}. This effect of E_2 is consistent with the findings that ovarian hormone loss increased I_{Ks} density as mentioned above [69]. In dogs, protein levels of $K_{ir}2.1$ and $K_V4.3$ that mediate I_{K1} and I_{to}, respectively, were significantly higher in 4-week DHT-treated OVX females and intact males than E_2-treated ORCH males and intact females [21]. Expression level of $K_V1.4$ which also mediates I_{to} was also higher in DHT-treated OVX females than E_2-treated ORCH males—a difference that almost reached statistical significance. Altogether, these results provide evidence that chronic manipulation of E_2 affects I_{CaL}, I_{NCX}, I_{Kr}, and I_{KS}, whereas chronic manipulation of DHT affects I_{K1}, I_{Kr}, I_{to}, and I_{CaL}.

Guinea pigs have also been used as animal models to explore sex differences in ventricular repolarization mechanisms. Like humans, female guinea pigs show longer ventricular APD than male guinea pigs [73,74]. Ventricular myocytes of female guinea pigs have higher level of functional K_{ATP} channels than male myocytes [75]. Activation of K_{ATP} channels is a part of the endogenous cardioprotective signaling that promotes cellular survival under severe metabolic stress conditions, and the higher level of K_{ATP} channels in female cells may be a factor that leads to sex differences in the incidence of cardiovascular disease. To understand the influence of endogenous ovarian hormones on ventricular repolarization, James et al. recorded from ventricular myocytes of intact male and female guinea pigs, with the latter group separated into two stages of estrus cycle: day of estrus (presumably high E_2) and 4 days postestrus (presumably elevated P_4-to-E_2 ratio) [73]. The results showed that myocytes from females on the day of estrus had longest APD, followed by those from females 4 days postestrus then those from intact males (Fig. 3.6). Density of I_{K1} was significantly larger in male cells than female cells from both estrus stages. Density of delayed rectifier tail currents (a mixture of I_{Kr} and I_{Ks}) and I_{CaL} were also larger in male cells, followed by day of estrus cells then 4 days postestrus cells. Another study also showed that APD was longer in female cells than in male cells from intact guinea pigs [74]. However, different from what James et al. reported, Mason et al. found that I_{CaL} was larger in female cells, as was the Ca^{2+} content in SR. In fact, following Ca^{2+} channel block, sex difference in APD was abolished. The study did not find a difference in I_{K1}, I_{Kr}, and I_{Ks}. It is unclear what contributed to the opposite results between these two studies on I_{CaL}. Given that female guinea pigs experience cyclic fluctuations of ovarian hormones, it is possible that pooling data from female animals in different stages of estrus cycle averaged out sex hormones' effects on some cardiac ion channels.

In terms of the net impact of chronic sex hormone treatment on ventricular repolarization and susceptibility to ventricular arrhythmias, results from studies of hormone-

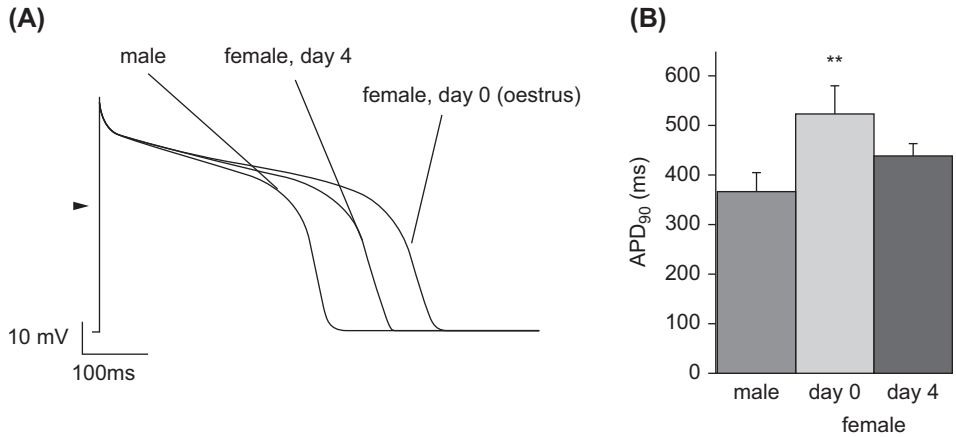

FIGURE 3.6 Sex differences in action potential duration (APD) from guinea pig ventricular myocytes. (A) Traces show representative time-averaged APs recorded from left ventricular myocytes from male, female day 0 (estrus), and female day 4. Traces represent the average of 10 consecutively recorded APs. (B) Mean APD_{90} from male (n = 12), female day 0 (n = 11), and female day 4 (n = 10) myocytes. $^{**}P < .05$ compared to male in a Student–Newman–Keuls posthoc test. *This figure is reprinted by permission from Springer Nature: James AF, Arberry LA, Hancox JC. Gender-related differences in ventricular myocyte repolarization in the Guinea pig. Basic Res Cardiol 2004;99:183–92. Copyright 2003.*

treated gonadectomized or intact rabbits are generally consistent, demonstrating that relative to controls, chronic DHT treatment is associated with smaller baseline APD [76,77] or QT interval [68], reduced degree of I_{Kr} blocker–induced APD [77,78] or QT prolongation [66,68], and decreased the tendencies of ventricular arrhythmia at the cellular level [76–78] (Fig. 3.7). Fewer rabbit studies have examined the effects of chronic E_2 treatment. Nonetheless, the results are generally in the opposite direction as the DHT treatment, with E_2 producing larger baseline APD [76] or QT interval [66], enhancing the degree of I_{Kr} blocker–induced APD [76] or QT prolongation [66], and promoting ventricular arrhythmias at the cellular level [76] relative to controls. Note that in these studies, DHT's effects were apparent in both female [66,76,77] and male rabbits [68,78], whereas E_2's effects were only apparent in the female [66,76] and not male rabbits [78]. In fact, using ORCH male rabbits treated with DHT or E_2 for 4–5 weeks, Pham et al. reported that the extent of APD prolongation and incidence of EAD induced by dofetilide was inversely related to the serum DHT level but had no relation with the serum E_2 level [78]. However, the same study also showed that ovarian hormone loss for 2 weeks in OVX female rabbits significantly reduced the extent of dofetilide-induced APD prolongation and incidence of EAD, suggesting that endogenous ovarian hormones also modulate proarrhythmia risk level in female cells. Whether these hormones include E_2 or not was unclear as the study did not test E_2 treatment in OVX female rabbits. Results from Fulop et al. also suggest that E_2's effect on ventricular repolarization is sex-specific. DHT treatment in OVX female dogs shortened QT and QT_C intervals and reduced the extent of dofetilide-induced QT_C prolongation, whereas E_2 treatment in ORCH male dogs led to no change in baseline QT_C interval or the extent of dofetilide-induced QT_C prolongation [21]. These results, coupled with studies mentioned earlier that showed $Ca_V1.2$ and NCX1 activities were upregulated by E_2 treatment in female but not male myocytes of rabbits [22,23] and humans [20], strongly suggest that genomic effects of E_2 on cardiac ion channels, ventricular repolarization, and arrhythmia propensity are sex-specific. Progesterone receptor (PR) is a known E_2-regulated gene. A study that used human atrial tissues grown in culture for 24 h found that even E_2's genomic

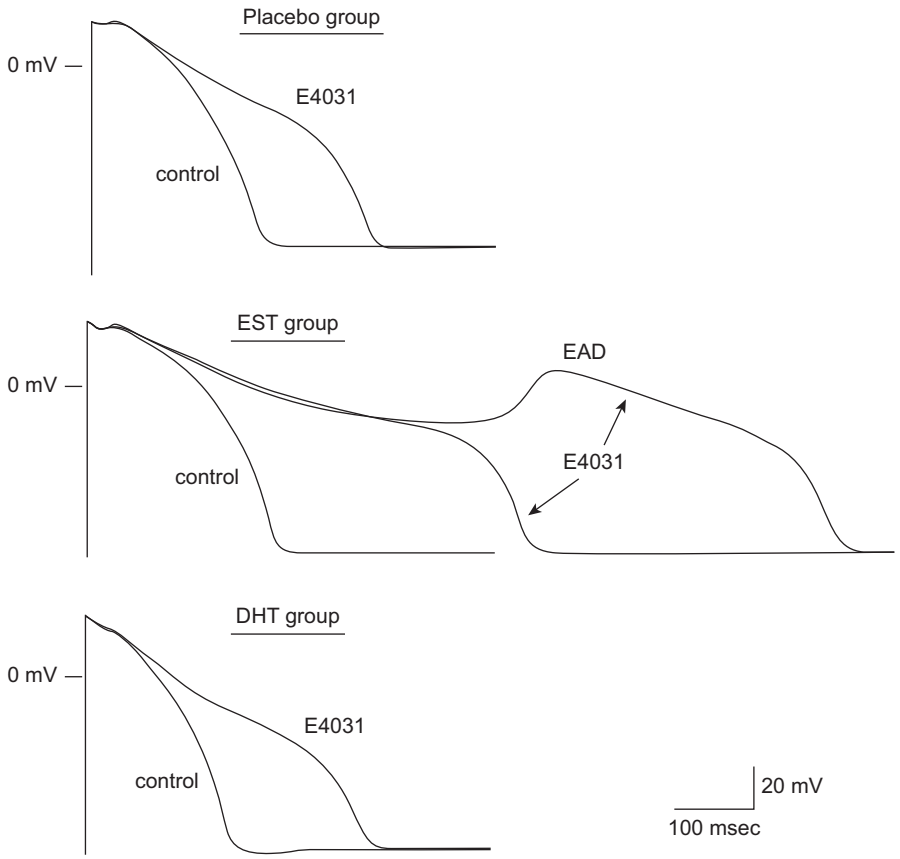

FIGURE 3.7 Representative experiments of the effects of E–4031 on papillary muscles from OVX female rabbits treated with placebo, estradiol (EST), or DHT. Note that action potential duration prolongation of the estradiol-treated group was greater than others and EAD was induced. Basic cycle length was 2 s. *This figure is reprinted by permission from ASPET, and is from Hara M, Danilo Jr P, Rosen MR. Effects of gonadal steroids on ventricular repolarization and on the response to E4031. J Pharmacol Exp Ther 1998;285(3):1068–72.*

regulation of PR is sex-specific. Following 24 h of E_2 (10 nM) treatment, PR mRNA and protein levels were upregulated in female but not in male tissues [65].

In OVX female animals, P_4 was also reduced following the surgery. Like ER, PR is also a ligand-activated transcription factor that regulates gene expression and mediates the genomic and nongenomic actions of progestins. Whether P_4 affects cardiac ion channels via genomic mechanism or not is currently unknown and should be addressed in future studies to better understand the biology underlying ventricular repolarization and arrhythmia susceptibility differences between men and women.

Acute effects of sex hormones on cardiac ion channels and ventricular repolarization

Sex hormones also regulate cardiac ion channels in an acute fashion, without involving changes in mRNA or protein synthesis. These rapid effects require continued presence of sex hormones and occur in a membrane-localized fashion either via activation of specific cellular signaling cascades or through hormone binding directly to ion channel proteins themselves. To help interpret whether acute effects of sex hormones on cardiac ion channels are likely to occur under physiological conditions, Table 3.1 provides concentrations of E_2, P_4, DHT, and T reported for adult men and women from different studies.

Recordings from guinea pig ventricular myocytes from both sexes showed that E_2 at 10−30 μM did not affect AP amplitude [79,80], maximum AP upstroke velocity [79,80], or RMP [79−81], suggesting no effect on I_{Na} or I_{K1}. Additional studies using CHO cells overexpressing $Na_V1.5$ channels [82] and guinea pig ventricular myocytes [80] confirmed that E_2 had marginal effects on these two currents. Instead, E_2 at 10−100 μM acutely inhibited I_{CaL} [60,79−81,83] without altering channel gating [60,81]. E_2's inhibition of I_{CaL} was independent of sex [60], occurred rapidly (seconds to <1 min) [80,81,83], and was reversible upon E_2 washout [60,80,81,83], demonstrating the nongenomic nature of this effect. In the micromolar range, E_2 has been reported to inhibit I_{Ks} in guinea pig ventricular myocytes [80], $K_V7.1$/minK current (thought to reflect I_{Ks}) in overexpressing CHO cells [82], I_{Kr} in guinea pig ventricular myocytes [80], and hERG current that reflects I_{Kr} in overexpressing HEK cells [84]. As Table 3.1 shows, the physiological concentration of E_2 in women is in the subnanomolar to nanomolar range (0.06−2.75 nM [85,86]). Even with clomiphene treatment of infertility, E_2 level reached 5.0 ± 1.4 nM only [55]. Thus, it is unclear how acute effects of E_2 on I_{Kr}, I_{Ks}, and I_{CaL} that required micromolar concentration could contribute to regulate ventricular repolarization. However, in contrast to other studies, Kurokawa et al. reported observing acute inhibition of I_{Kr} by E_2 in female guinea pig ventricular myocytes at concentration as low as 1 nM [87]. This effect was caused by a shift in hERG channel gating, required interaction of E_2 with a common drug-binding residue at the inner cavity of hERG channels, and did not involve ER activation. In the presence of E_2, sensitivity of hERG current suppression and QT prolongation by E4031 that also acts on the same residue was enhanced. These results raise a possibility that E_2 may be proarrhythmic because it can increase sensitivities of some drugs to inhibit I_{Kr}. At 300 nM, E_2 inhibited I_{CaL} and enhanced I_{Ks}, the latter effect requiring ER activation. It is unclear why Kurokawa et al. could detect an acute E_2 effects at low nanomolar concentration range. Additional studies are needed to confirm these results.

Regarding the overall acute effect of E_2 on myocyte functions, conflicting evidence have been presented. Two studies using guinea pig ventricular myocytes found that E_2 at 10−30 μM produced negative inotropic effect by reducing intracellular Ca^{2+} transient [81], shortened APD [79,81], and reduced the extent of APD prolongation and EADs induced by a proarrhythmic agent endothelin-1 [79]. In contrast, Tanabe et al. found that E_2 at 30 μM prolonged APD in guinea pig ventricular myocytes [80]. Finally, the study by Kurokawa reported bidirectional effects of E_2 on ventricular repolarization in guinea pig ventricular myocytes and hearts: at 1 nM, E_2 prolonged APD and QT_C interval; at 300 nM, E_2 reduced APD and QT_C interval [87]. These effects were attributed to E_2's inhibition of I_{Kr} at 1 nM and enhancement of I_{Ks} at 300 nM, respectively.

Fewer studies have examined the acute effects of P_4 and androgens on cardiac ion channels. One study showed that acute exposure to P_4 rapidly shortened APD in female guinea pig ventricular myocytes from animals in two estrus stages that correspond to low and high serum P_4 levels [64]. There was no difference in P_4's effects on these two stages. Under basal condition, APD shortening by P_4 was attributable to an enhancement of I_{Ks}, with no effect on I_{CaL}. Under β-adrenergic stimulation to mimic sympathetic nervous system (SNS) activity, P_4 inhibited cAMP-enhanced I_{CaL} through changes in channel gating without affecting I_{Ks} (Fig. 3.8). These results demonstrate that the mechanism underlying APD shortening by P_4 is under the control of SNS activity. The acute effects of P_4 on I_{CaL} and I_{Ks} can be observed at concentrations within the physiological range, suggesting that these mechanisms may contribute to the protective effect of P_4 against QT prolongation as suggested by human studies [9,42,47−50]. The inhibitory effects of P_4 on I_{Ks} and I_{CaL} are indirect, requiring activation of PR and nitric oxide (NO) release via acute activation of endothelial NO synthase (eNOs). As mentioned above, PR is a known genomic target of E_2. *That the expression level of PR is regulated by E_2 suggests that E_2 can*

TABLE 3.1 **Sex hormone levels in adult men and women.**

	Women		Men	References
Estradiol (E_2) (pM)	Follicular		36.7–183.6	[85]
	Early	73.4–550.7		
	Late	146.84–1284.9		
	Midcycle	550.7–2753.3		
	Luteal	110.13–1651.95		
	Postmenopause	≤73.4		
	Mean levels of days	1–6 150–370		[90][a]
	Preovulatory peak	690–2120		
	Luteal maximum	480–1180		
	Mean luteal phase level	300–710		
	Menstruation	170.1 ± 116.8		[91]
	Late follicular	533.5 ± 289.6		
	Luteal	369.7 ± 126.9		
	Menses	105 ± 34		[43]
	Preovulatory phase	750 ± 277		
	Early follicular	279		[42]
	Luteal	253.3		
	Follicular	150.7 ± 48.3	164.8 ± 47.7	[86]
	Ovulatory	676.2 ± 13.9		
	Postmenopause	60.5 ± 34.7		
Progesterone (P_4) (nM)	Mean levels of days	1–6 1.2–4.4		[90][a]
	Luteal maximum	32–92		
	Mean luteal	15–42		
	Mean during cycle	8–24		
	Menstruation	6.5 ± 12.1		[91]
	Late follicular	2.5 ± 1.3		
	Luteal	40.6 ± 19.2		
	Early follicular	1.59		[42]
	Luteal	16.7		
	Follicular	2.2 ± 1.1	2.5 ± 0.9	[86]
	Ovulatory	10.5 ± 18.0		
	Postmenopause	0.82 ± 0.57		
5-α Dihydrotestosterone (DHT) (nM)	0.2–1.0		0.9–2.6	[85]
			0.1–2.0	[88]
Testosterone (T) (nM)	Premenopause	0.5–2.4	9–34.7	[85]
	Postmenopause	0.2–1.8		
	Follicular	0.6 ± 0.3	16.32 ± 5.5	[86]
	Ovulatory	0.9 ± 0.5		
	Postmenopause	0.6 ± 0.3		
			13.2–29.8	[88]

[a]*Values reported are the limits covering 91% of 68 subject [90].*

indirectly affect ventricular AP by regulating P_4's acute effects on ventricular ion channels.

Regarding androgens, DHT at 10 nM did not affect hERG current or the potency of E4031 to block hERG channels in HEK cells [87]. However, an inhibitory effect was observed at 30 nM, although this was beyond the physiological range (0.1–2.6 nM in men and women [85,88]). In male guinea pig ventricular myocytes, one study reported that 10–30 μM T was without effect on APD or I_{CaL} [81]. However, another study that also used guinea pig ventricular myocytes found that T application rapidly shortened APD in the nanomolar range [89], which

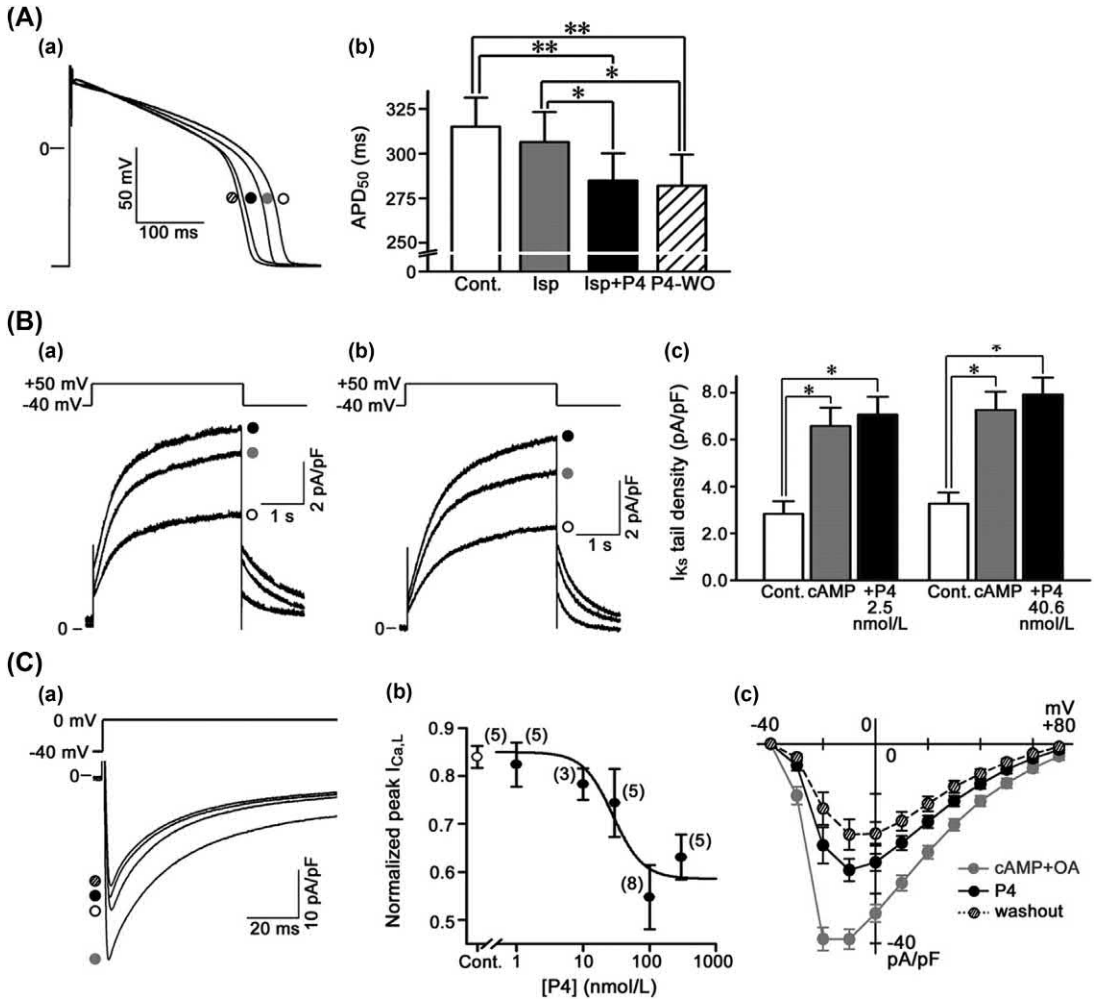

FIGURE 3.8 Effects of P_4 under conditions mimicking sympathetic nervous system stimulation. (A) Effects of P_4 on action potential duration (APD). (a and b) Representative recordings of AP (a) and APD_{50} (n = 8; b) at baseline (open symbols), after Isp or isoproterenol application (*gray symbols*), after additional application of 100 nM P_4 (*black symbols*), and after a washout of P_4 (*hatched symbols*). (B) Effects of P_4 on I_{Ks}. a through c, Representative recordings of I_{Ks} at 2.5 nM P_4 (a), those at 40.6 nM P_4 (b), and averaged I_{Ks} tail density (c) just after establishment of whole-cell patch-clamp configuration (*open symbols*), after stabilization of effects of cAMP and okadaic acid (*gray symbols*), and after subsequent application of 2.5 nM (n = 8) or 40.6 nM (n = 7) P_4 (*black symbols*). (C) Effects of P_4 on $I_{Ca,L}$. (a), Representative recordings of $I_{Ca,L}$ just after establishment of whole-cell patch-clamp configuration (*open circle*), after stabilization of effects of cAMP and okadaic acid (OA; *gray circle*), after subsequent application of 40.6 nM P_4 (*black circle*), and after a 10-min washout (*hatched circle*). (b), Dose−response curve for suppression of $I_{Ca,L}$ inward peak by P_4. Continuous line is the result of fitting to Langmuir's isotherm. Numbers in parentheses indicate the number of data. (c), Effects of P_4 (40.6 nM) on I−V curves (c; n = 7). In A and B, statistical significance was analyzed with an ANOVA followed by Bonferroni's test. $*P < .05$; $**P < .01$. *This figure was adapted with permission from Wolters Kluwer Health, Inc.: Nakamura H, Kurokawa J, Bai CX, Asada K, Xu J, Oren RV, Zhu ZI, Clancy CE, Isobe M, Furukawa T. Progesterone regulates cardiac repolarization through a nongenomic pathway. Circulation 2007;116(25):2913−22 (https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.107.702407).*

is within the physiological range (up to 34.7 nM in men [85]). This effect was attributed to I_{Ks} enhancement under basal condition and I_{CaL} inhibition under cAMP-stimulated conditions, and involved activation of the T receptors and two distinct cellular signaling cascades associated with eNOs activation. These results suggest that acute effects of T on cardiac ion channels may contribute to control QT_C interval in men.

In summary, E_2, P_4, DHT, and T have varying acute effects on I_{CaL}, I_{Ks}, and I_{Kr}. The effects of P_4 and T were observed within the physiological concentration range of women and men, respectively, suggesting that these effects may contribute to regulate APD and QT_C interval in humans. The acute effect of DHT on hERG current required concentrations outside the physiological range, as was the effect of E_2 on hERG current as demonstrated in most of the studies. Thus, the acute mechanisms described for these two hormones may not contribute to sex differences in ventricular repolarization.

Sex hormone regulation of ion channels and ventricular repolarization

Based on the results from animal studies summarized in this chapter, the following schemes are proposed to explain regulation of ventricular repolarization by sex hormones in males and females. In female myocytes, chronic exposure to circulating E_2 level affects the magnitude of I_{CaL}, I_{NCX}, and I_{Ks} via genomic or long-lasting nongenomic mechanisms. Elevated level of E_2 increases I_{CaL} and I_{NCX}, and reduces I_{Ks}, leading to a cellular environment that prolongs APD and promotes arrhythmia. Female ventricles have reduced levels of transcripts and proteins that mediate I_{Kr} and I_{K1}, though it is unclear whether these effects are hormone-mediated. P_4's genomic mechanism is currently unclear. However, P_4 acutely increases I_{Ks} under basal condition and decreases I_{CaL} under β-adrenergic stimulation, thereby countering E_2's genomic effects by limiting APD and reducing proarrhythmia propensity. Acute effects of P_4 require PR activation, and E_2 regulates the level of PR. Thus, acute effects of P_4 may be viewed as a negative feedback mechanism that stabilizes ventricular repolarization in women during cyclic changes of E_2 level. T and DHT levels are very low in women, and these androgens are unlikely to play a role in ventricular repolarization in women. In male myocytes, DHT regulates the levels of I_{Ks}, I_{Kr}, and I_{K1} via genomic mechanism, thereby increasing the basal repolarization drive. Acutely T increases I_{Ks} under basal condition and reduces I_{CaL} under β-adrenergic stimulation. Thus, in male cells, genomic and nongenomic mechanisms of androgens both serve to reduce inward current and increase outward currents. This may explain the reduced ventricular repolarization and proarrhythmia risk in men relative to women.

Conclusions

Women have longer QT and QT_C intervals than men and are generally at higher risk of long QT-associated arrhythmias such as Torsade de Pointes. Evidence from human and animal studies suggests that these sex differences arise in part from complex regulations of cardiac ion channels by male and female sex hormones, through both genomic and acute mechanisms. Research shows that sex hormones affect nearly all the major ionic currents in ventricular myocytes, in a sex-specific and region-dependent manner. More research is necessary to establish the link between sex hormones' effects on ventricular ion channels and clinical manifestations of arrhythmias in men and women. As seen in Table 3.1, reference sex hormone levels vary widely across and within studies, suggesting large individual variability. Accordingly, chronic and acute mechanisms of sex hormones on ion channels may be expressed differently in different people based on their hormone levels. Future basic science studies using animal models and clinical studies of ventricular arrhythmia mechanisms would benefit from quantifying sex hormone levels to allow for mechanistic data interpretation. Better understanding of the cellular mechanisms that underlie sex differences in ventricular repolarization and susceptibility to ventricular arrhythmias is important and should contribute to improve patient care by allowing more accurate assessment of drug risk in men and women.

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Chapter 4

Atrial and ventricular tissue electrophysiology

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Atrial and ventricular heart tissue is composed of contractile cardiac muscle cells (cardiomyocytes), blood vessels, autonomic nerves, and connective tissues (Fig. 4.1). Several mechanisms have been hypothesized to underline sex differences in cardiac electrophysiology, including differences in cardiac ion channel expression levels and function; differences in autonomic tone and its alteration induced by sex hormones; and differences in three-dimensional architecture including heart size and cell-to-cell coupling. Clinically observable differences may stem from alterations in one or more of these factors. Sex differences in ion channel expression and hormonal effects are covered in other chapters of this book. Here, we offer a brief introduction to the structure and electrophysiology of atrial and ventricular tissue and then discuss some examples of sex-related differences reported in the literature. Specifically, sex-based differences related to the autonomic nervous system, sinoatrial node function, excitation–contraction coupling, action potential duration (APD), extracellular matrix structure, and cardiac tissue remodeling will be discussed.

Heart size

Heart sizes are similar in girls and boys [1]. After puberty, absolute heart mass is greater in men than in women by about 15%–30% [2].

Autonomic nervous system

The autonomic nervous system governs the heart output with two opposite branches of the system working collaboratively: stimulation of the sympathetic branch of the system is responsible for increase in heart rate and cardiomyocyte contractility, while parasympathetic stimulation leads to decrease heart rate and cell contractility. Autonomic nervous system plays important role in many arrhythmias, both in the atria and in the ventricles [3–5].

Sympathetic nerves innervate atrial and ventricular myocardium. Largest populations of cardiac ganglia are located near the sinoatrial and atrioventricular nodes of the heart with smaller collections of ganglia found on the superior left atrial surface, the internal septum, and the atrial appendage–atrial junctions (Fig. 4.2) [6]. The average numbers of ganglia in human hearts of either sex was estimated at 458 $\pm$ 43 in atrial tissues and 88 $\pm$ 7 ganglia in ventricular tissues with the estimated total number of intrinsic ganglionic neurons of 14,000 in a heart with no sex differences reported [7]. In animal studies, sex differences in cardiac ganglia were found in mice using neurochemical analysis [8]. In particular, neurotransmitter levels for norepinephrine (NE) and acetylcholine (ACh) were assessed and found generally similar between the sexes, except for the right atrium, where females had significantly higher levels of ACh. Furthermore, the levels of the main NE metabolite, dihydroxyphenylglycol in the right atrium, were also higher in females, suggesting higher NE turnover.

Governed by the autonomic nervous system, the basal heart rate in women is higher than in men [9,10]. This disparity is still observed in young girls versus boys, though to a smaller extend, suggesting that hormones alone do not explain the differences in heart rate. Furthermore, in these studies, the basal heart rate was different in men and women even after autonomic system was blocked with beta blockers or parasympathetic system blockers, suggesting that some of the sex differences in heart rate are in fact "intrinsic" and not related to differences in autonomic tone or hormones. In addition to these

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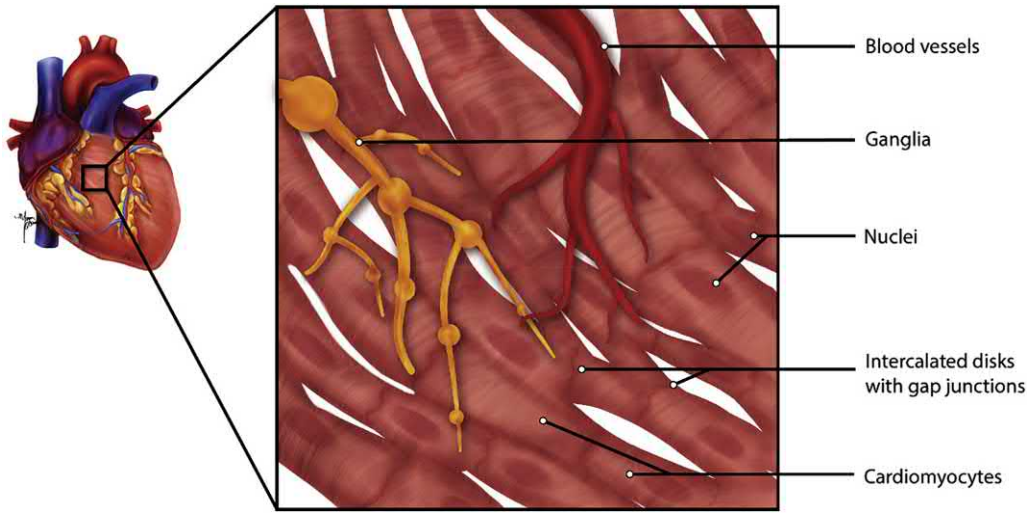

FIGURE 4.1 Schematic of cardiac tissue. Cardiomyocytes connect through gap junctions, forming cardiac tissue, innervated by sympathetic ganglia and permeated by capillary blood vessels. *Illustration by Megan O'Connell and Andrea Kim.*

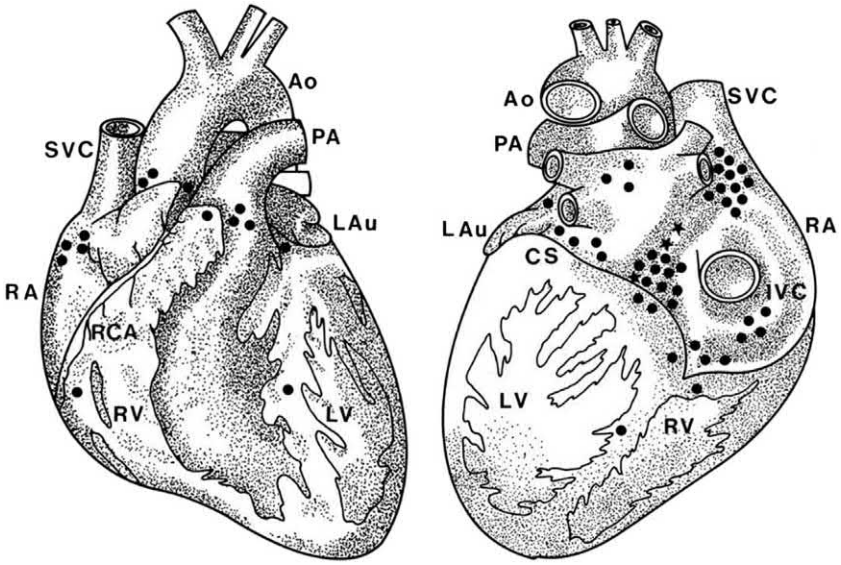

FIGURE 4.2 Anterior (left) and posterior (right) view of adult human heart showing topography of the cardiac ganglia. Ganglia are concentrated primarily at base of aorta (Ao) and pulmonary artery (PA). Para-sinoatrial (SA) nodal ganglia are concentrated primarily lateral to the right pulmonary veins. The para-atrioventricular (AV) nodal ganglia are on the epicardial surface superior to the coronary sulcus (CS) and within the interatrial septum. *Reproduced with permission from Singh S, Johnson PI, Lee RE, Orfei E, Lonchyna VA, Sullivan HJ, et al. Topography of cardiac ganglia in the adult human heart. J Thorac Cardiovasc Surg 1996;112(4):943–53.*

differences in the heart rate, the variability of the heart rate (measured by RR interval variability) is also different in males and females [11].

It has also been reported that male cardiomyocytes isolated from adult rats have a higher β-adrenergic receptor density than female cells and thus have an enhanced response to β-adrenergic stimulation [12]. Similar disparities were observed in isolated adult rabbit hearts, where isoproterenol response was significantly lower in female hearts, especially at the higher beating rate [13]. These authors further report that the reduced β-adrenergic responsiveness of female hearts was also associated with reduced arrhythmogenicity.

Sinoatrial and atrioventricular nodes

Autonomic nerve fibers extend through heart tissue with the right vagus nerve primarily innervating the sinoatrial (SA) node and the left vagus nerve innervating the atrioventricular (AV) node. Autorhythmic nodal cells are rhythmically

discharging governing the electrical signal propagation leading to heart contraction while SA node depolarization rate is constantly being affected by innervations from both the sympathetic and parasympathetic nervous system. Women have greater SA node automaticity, with a shorter sinus cycle length [14]. Sinus node recovery time and atrial refractory period are significantly longer in males compared to age-matched females (Fig. 4.3) [15]. These differences in clinical electrophysiology might be underlined by sex-related differences in the density of metabolically active cells in sinoatrial node. At least one study has reported by measuring phosphorus content in the isolated sinoatrial node tissues derived from Japanese monkeys that the density of the active cells in SA node is significantly higher in females than in males [16].

Excitation–contraction coupling

The electrical stimuli from the sinoatrial node is translated into cardiomyocyte contraction through excitation–contraction coupling governed by Ca^{2+} influx through the voltage-sensitive L-type Ca^{2+} channels and subsequent release of sarcoplasmic reticulum Ca^{2+} storage through the ryanodine receptor. Ventricular cardiomyocytes are rich in special transverse tubules (T-tubules) that represent extensions of the cell membrane (sarcolemma) that penetrate into the center of the cardiomyocyte, helping to conduct impulses from the cell membrane down into the sarcoplasmic reticulum. There are fewer T-tubules in atrial cardiomyocytes, and almost no T-tubules in nodal cells or in Purkinje fibers. Massive release of Ca^{2+} from sarcoplasmic reticulum allows Ca ions to bind to the myofilaments, specifically to troponin C, resulting in contraction of cardiomyocytes. Sex differences in mechanisms of cardiac excitation–contraction coupling have been reported in animal models (see Ref. [17] for review). In isolated rat ventricular cardiomyocytes, despite similar Ca^{2+} current density, Ca^{2+} transients were smaller in females than in males. Furthermore, the excitation–contraction coupling gain (the ratio of Ca^{2+} release/inward Ca^{2+} current) was also significantly lower in females than in males [18]. But in another study in guinea pig heart pea L-type Ca^{2+} current was larger in females suggesting that sex differences in APD result from variation in the kinetics of L-type Ca^{2+} current stemming from alterations to Ca^{2+} release (Fig. 4.4) [19]. Cyclic adenosine monophosphate (cAMP)/PKA is an important signaling pathway in excitation–contraction coupling. It has been shown that estrogen suppresses sarcoplasmic reticulum Ca^{2+} release and that this is regulated, at least in part, by the cAMP/PKA pathway, improving our understanding of female-specific cardiomyocyte mechanisms [20]. Blocking Ca^{2+} release from the sarcoplasmic reticulum has larger impact on isoproterenol-induced changes in female compared with male cardiomyocytes [21].

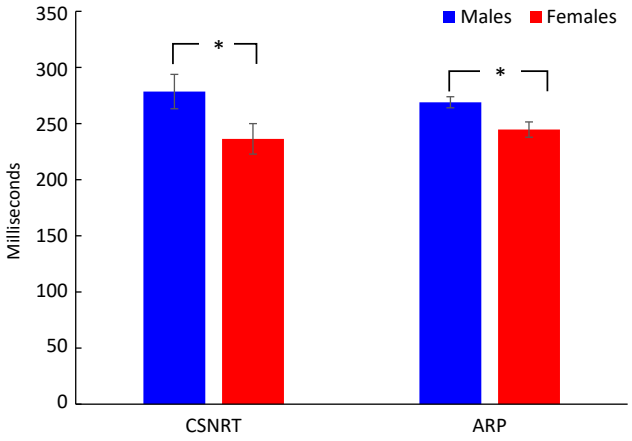

FIGURE 4.3 Sex differences in corrected sinus node recovery time (CSNRT) and atrial refractory period (ARP), error bars represent ± SEM, $*P < .05$. *Figure generated based on data previously published Sanjeev S, Karpawich PP. Developmental changes in sinus node function in growing children: an updated analysis. Pediatr Cardiol 2005;26(5):585–588.*

Cardiac action potential

Cardiac action potential is a change in cardiomyocyte membrane potential due to inward and outward currents of ions across the membrane. The sex-specific variations in ion channels expression are believed to lead to different atrial and ventricular action potential profiles between males and females (Fig. 4.2) and to ultimately translate to differences in electrocardiographic parameters recorded from male and female patients in clinic (see Ref. [22] for review). Specifically, in adult human, female hearts have reduced expression of potassium repolarizing channels [23], L-type calcium current is higher in female base (but not apex) cardiomyocytes [24], and sodium current is higher in female epicardial and endocardial cells (but not in midmyocardial cells). [25], leading to differences in morphology and duration of cardiomyocyte action potential and ultimately underlying longer QT intervals, and shorter QRS, PR intervals, and P-wave duration observed in female electrocardiogram (Fig. 4.5) [26,27].

Direct measurements of human cardiomyocyte action potentials are possible from nontransplantable or end-stage failing hearts, but these samples are available in very limited quantities. There thus exists a need for an alternative cardiovascular physiology model. Sex-related findings on action potential parameters in primary cardiomyocytes isolated from human and animal hearts as well as human cardiomyocytes, derived from stem cells, and experiment-based computer simulations are reviewed in this section.

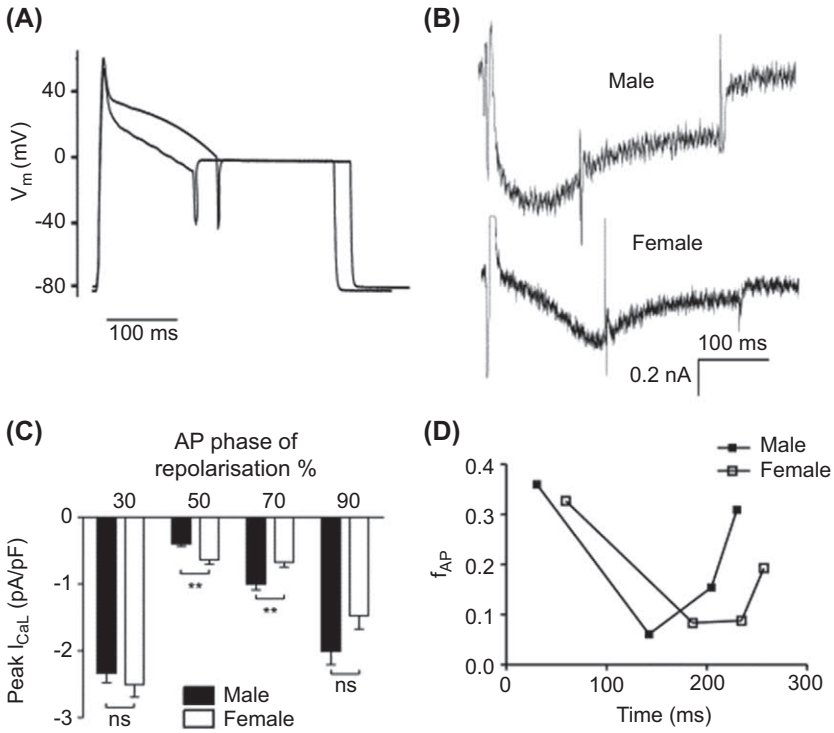

FIGURE 4.4 Gender differences in L-type calcium channel (I_{CaL}) availability during action potential clamp. (A) Shows typical stimulus files and (B) representative currents elicited from these protocols. (C) Illustrates pooled data ICaL at 30%, 50%, 70%, and 90% repolarization. (N = 12−16; $*P < .05$, $**P < .01$). (D) Illustrates the differences in availability (fAP) of ICaL during male and female action potentials. *Reproduced with permission from Mason SA, MacLeod KT. Cardiac action potential duration and calcium regulation in males and females. Biochem Biophys Res Commun 2009;388(3):565−70.*

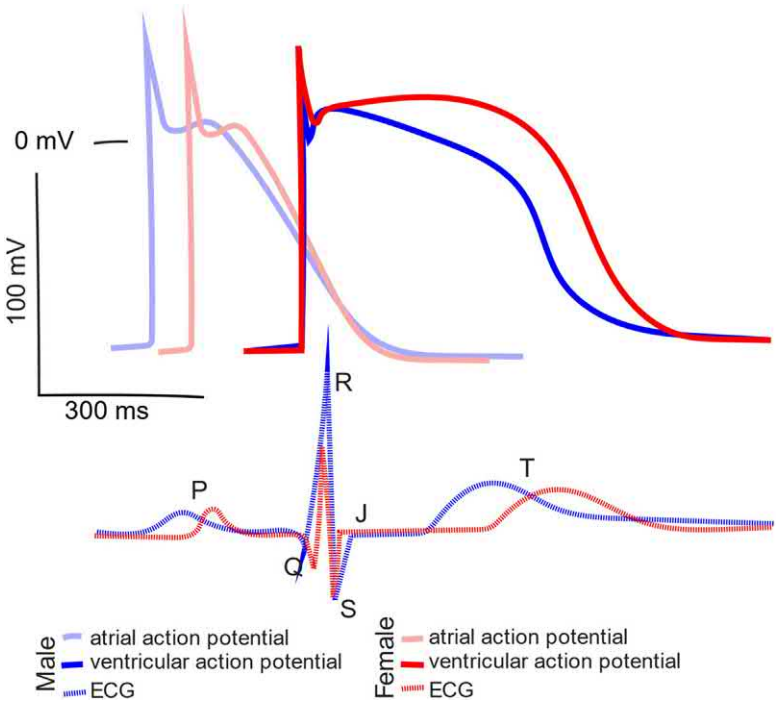

FIGURE 4.5 Sex-specific atrial and ventricular action potentials. *Figure courtesy of Anna Gams, Department of Biomedical Engineering, Efimov Lab, George Washington University, redrawn from Zipes DP, Jalife J, Stevenson WG. Cardiac electrophysiology: from cell to bedside 2018; Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on Atrial cardiomyopathies: definition, characterisation, and clinical implication. J Arrhythm 2016;32(4):247−278.*

Cardiomyocytes isolated from human hearts

Action potential recordings in ex vivo human heart preparations are scarce, and even when APD is recorded in both, cardiomyocytes isolated from male and female hearts, the reported data often contain averaged parameters, but no sex-specific data [30,31]. In Ref. [32], authors isolated midmyocardial left ventricular cardiomyocytes from explanted hearts of five male and five female patients undergoing cardiac transplantation and recorded action potentials using whole-cell patch-clamp technique. The results were consistent with the hypothesis that the long-observed longer QT interval duration in female versus male humans is underlined by longer cardiomyocyte APD. Female cardiomyocytes had significantly longer APD at each of the repolarization stages, including APD at 90% repolarization (APD_{90}) of 866 ± 60 ms in female cardiomyocytes versus 672 ± 43 ms in male cardiomyocytes at 2-s cycle length ($P < .05$) and 375 ± 29 ms (female) versus 271 ± 36 ms (male) at 20% repolarization (APD_{20}). There were no statistically significant differences observed in action potential properties beyond APD in this study, including cell capacitance, resting membrane potential, maximal action potential amplitude, maximal depolarization velocity, or maximal repolarization velocity.

Recorded ex vivo atrial action potentials from female and male patients in atrial fibrillation did not exhibit significant differences in shape, except that action potentials from women had slower upstroke velocity [33]. 652 action potentials were recorded from right atrial appendage preparations from 520 male and female patients.

Animal-isolated cardiomyocytes and tissues

Use of adult cardiomyocytes isolated from the heart tissue of rats and other animals has been a golden standard for in vitro studies of cardiac electrophysiology since 1970s [34]. While APD_{90} is commonly regarded to be longer in females than in males in earlier studies, such supporting data were typically from studies in isolated cardiomyocytes at room temperature with slow (nonphysiologic) pacing rates; a closer review of the literature shows that studies are divided on whether APD or the QT interval in females is longer or similar to corresponding values in males. Studies conducted in intact tissue preparations at physiologic temperatures and pacing rates were more likely to show similar APDs in males and females (see Ref. [17] for review).

APD was measured in many animal models using various experimental samples and approaches. APD_{20}, APD_{50}, and APD_{90} in mice ventricle cardiomyocytes was significantly longer in females compared with male mice [35,36] and attributed to lower expression of potassium channels and smaller repolarizing currents in female cells. Furthermore, in orchiectomized mice, APD_{20}, APD_{50}, and APD_{90} as well as QTc intervals were all significantly longer than in control male mice, suggesting a role of androgen on repolarization. APD_{90} was reported to be 11% longer in female versus male rabbit cardiomyocytes paced at 1 Hz (672.7 ± 3.7 vs. 604.9 ± 3.6 ms, $n = 26$ (24 hearts), 29 (24 hearts), $P < .01$ for female vs. male) [21], while these sex-specific differences in rabbit action potentials were absent in young rabbits and abolished by gonadectomy [37]. APD of female cardiomyocytes was longer than that of male cells paced at the same slow rate in canine heart [38]. An animal study that took in account estrus cycle found that APD_{90} was longer in female guinea pig ventricular cardiomyocytes at as compared to that of a male on day 0 of the cycle, but at day 4 the duration was equal in both male and female cells, supporting role of hormones in sex-specific cardiac electrophysiology [39].

Human cardiomyocytes derived from stem cells

Relatively recently a new model of human cardiac electrophysiology became available to researchers. Discovered in 2007 [40], induced pluripotent stem cells (iPSCs) can be differentiated in multiple organ−specific cell types, including cardiomyocytes of various lineages, including ventricular-, atrial-, and nodal-like cardiomyocytes. Blood samples or skin biopsy samples for iPSC-derived cardiomyocytes production can be collected from adult consented subjects of either sex. The resulting sex-specific iPSC-derived cardiomyocytes are expected to carry genetic information of the donor, including sex-related differences as well as variations related to possible disease status (normal vs. genetic cardiovascular disease carriers). These cells have been proposed for disease modeling as well as an in vitro model for predicting drug-induced ventricular arrhythmias, Torsade de Pointes [41,42], as well as an integrated subject-specific model for prediction of an individual clinical response [43,44].

A few iPSC-based studies have been done so far that studied specifically the effects of donor's sex on the electrophysiological characteristics of resulting iPSC-derived cardiomyocytes. In one study, three male and three female commercially available iPSC-derived cardiomyocyte lines were used to measure baseline electrophysiological characteristics and drug-induced effects [45]. The authors matched male and female lines based on the baseline spontaneous beating rate and report female Fridericia rate-corrected [46], repolarization duration to be longer as compared to male, in two out of three pairs.

In our own unpublished experiments, we have recorded baseline characteristics of subject-specific iPSC-derived cardiomyocytes obtained from a larger sample of male and female young normal healthy subjects (7 women and 10 men) using voltage-sensitive dye optical

recordings of cellular APD at 37°C and compared these data to the clinical electrocardiographic recordings of QT interval in these subjects. While clinical Fridericia rate-corrected QTc duration was longer in female subjects (410 ± 14 ms in females vs. 388 ± 11 ms in males), the average cellular Fridericia rate-corrected ADPc was shorter in female subject–specific iPSC-derived cardiomyocytes (278 ± 31 ms in females vs. 304 ± 27 ms in males) (Fig. 4.6).

Donor-specific iPSC-derived cardiomyocyte technology is an exciting and promising new model in cardiac electrophysiology, but it needs thorough validation and verification to further develop iPSC-based assays and understand this approach limitations. Further development of the reprogramming and differentiation protocols is also needed to address known morphological and functional immaturity of iPSC cardiomyocytes as well as high variability in the characteristics of the cells developed in different laboratories.

In silico modeling

Mathematical models of human ventricular cardiomyocytes with sex-specific ion channel currents available from the experimental data predict longer APD in female cells, steeper APD–heart rate relationship, and greater susceptibility to early afterdepolarizations. Male cells, on the other side, are predicted to have more prominent phase-1 repolarization [47]. Mathematical models of male and female ventricular tissue that take into account differences in ion channel expression and hormone effects suggested that female susceptibility to alternans stems from longer action potentials and further confirms that increased incidence of ventricular arrhythmias (like Torsade de Pointes) has its roots in the sex-based differences in ventricular electrophysiology [48].

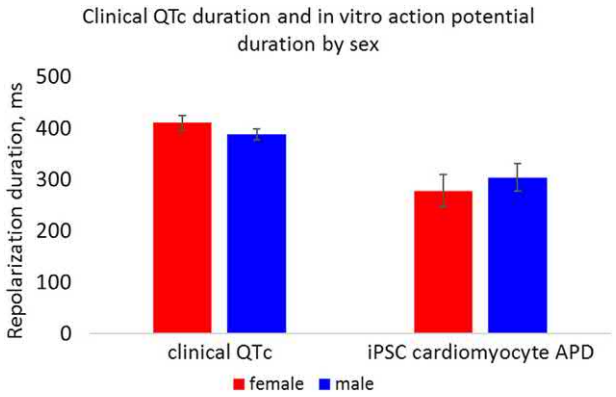

FIGURE 4.6 Fridericia rate-corrected QT interval duration in normal, healthy, young male and female subjects ($N_{female} = 7$, $N_{male} = 10$) compared to Fridericia rate-corrected action potential duration at 90% repolarization measured in subject-specific induced pluripotent stem cell–derived cardiomyocytes using voltage-sensitive optical recordings. Error bars represent ±1 SD.

Action potential dispersion

APD dispersion across heart wall is widely considered as potentially arrhythmogenic. Transmural gradient of repolarization time and APD was estimated from T-wave morphology in electrocardiograms of 5376 healthy men and women [49]. Both epi- and endo-cardiac APD was shorter in men than in women, by 18 and 14 ms, respectively. The estimated crossmural RT and APD gradients were the same in both sexes, but the duration of phase 2 plateau of the epicardial action potential was 19 ms longer in women.

Study using isolated cardiomyocytes from epi-, endo-, and mid-myocardium of canine hearts of both sexes found no differences in epi- and endo-APD, but the action potential of the cells derived from midmyocardium was significantly longer in female samples (e.g., at 1 Hz, female vs. male: 288 ± 21 vs. 237 ± 8 ms; $P < .05$), resulting in greater transmural APD heterogeneity in females [38]. Sex differences in transmural APD dispersion was concluded to be underlined by the differences in ionic currents in female and male hearts. Consistent with clinical and isolated cardiomyocyte studies, in silico modeling has also predicted larger transmural APD heterogeneity in females [47].

Much less is known about sex differences in APD gradients between the right ventricle and left ventricle, or between apex and base. Even when data seem to exist for animals of both sexes (see i.e., [50,51]), the sex-specific gradient data are not reported. There were no statistically significant differences in male and female ventricular action potentials (APD_{90}) or calcium transient duration (CaD_{80}) measured in either the left ventricle base (left) or apex (right) of adult rabbit hearts (Fig. 4.7) [13].

Contractility

Force–frequency relationship is an important intrinsic regulatory mechanism of cardiac contractility. In normal myocardium, the heart contractility force increases with the increase in heart rate [52]. The positive force–frequency relationship is maintained in absence of sarcoplasmic reticulum function in rabbit, but not in rat myocardium [53]. Positive force–frequency relationship is observed in both male and female cat isolated trabeculae, but at higher pacing frequencies (1.5 and 2.0 Hz), force produced by male trabeculae is significantly higher than that produced by trabeculae from females with a significant sex differences in the overall force–frequency response (30% higher in males) [54]. Consistent with these findings, isoprenaline, a beta-adrenergic agonist, induces significantly higher calcium transient increase in

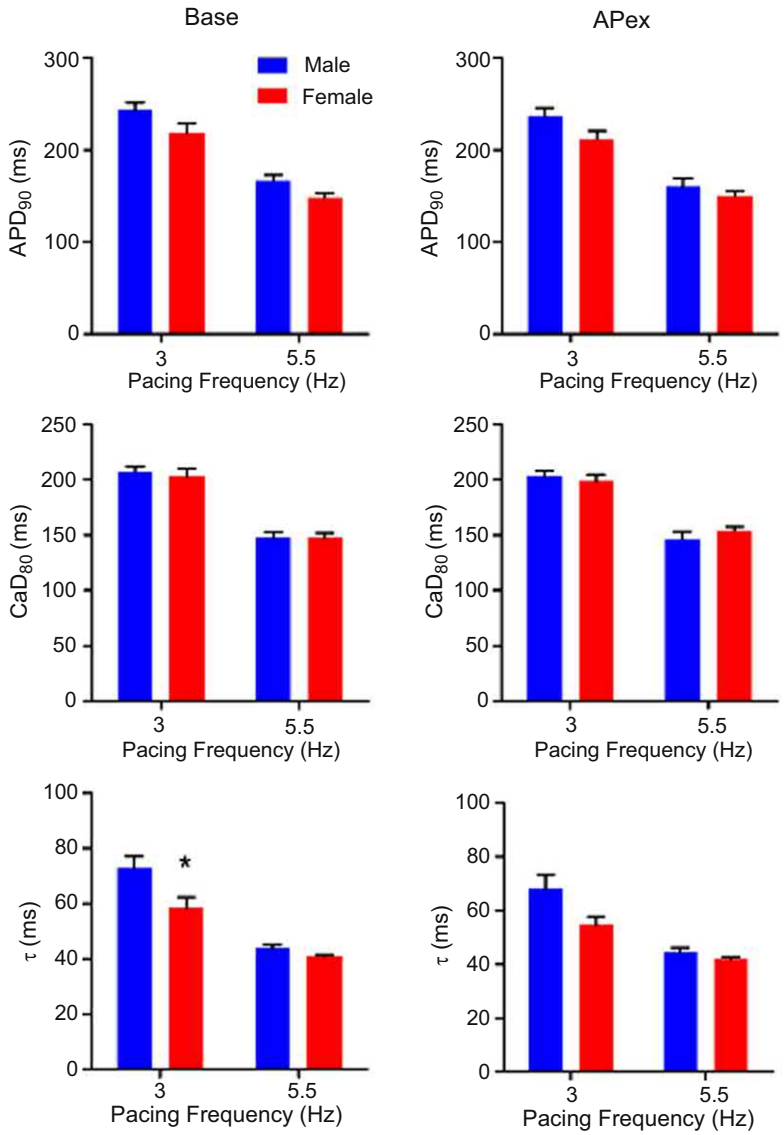

FIGURE 4.7 Sex differences in steady-state ventricular action potentials (APD_{90}) or calcium transient duration (CaD_{80}) measured in either the left ventricle base (left) or apex (right) were statistically insignificant in isolated rabbit hearts paced at 3 and 5.5 Hz. The time constant of calcium recovery was significantly lower at the base of hearts isolated from female rabbits and paced at 3 Hz but was not different at faster pacing rate (5.5 Hz). *Reproduced from open source publication Hoeker GS, Hood AR, Katra RP, Poelzing S, Pogwizd SM. Sex differences in beta-adrenergic responsiveness of action potentials and intracellular calcium handling in isolated rabbit hearts. PLoS One 2014;9(10):e111411.*

male rat isolated cardiomyocytes as compared with female cardiomyocytes [55].

Gap junctions

Cardiomyocytes attach to one another with specialized cell junctions called intercalated discs, forming strong mechanical links between cardiomyocytes and responsible for the tissue integrity. The electrical currents are transmitted from cell to cell through gap junctions. One role of gap junctions is to permit the passage, from cell to cell, of currents that are essential for action potential propagation through cardiac tissue. Gap junctions facilitate ion transfer between cells producing intracellular electrical coupling and allowing for the cells to contract in synchrony. Gap junctions are formed by membrane proteins known as connexins (Cx), with connexin 43 (Cx43) being predominant in the ventricular tissue. The abnormalities in Cx43 lead to conduction defects

and contractile dysfunction. It has been shown that Cx43 mRNA and protein expression were higher in female than male adult rat cardiomyocytes [56,57], thus favoring cardioprotection in female cardiomyocytes.

Extracellular matrix structure

Cardiomyocytes comprise 75% of the heart tissue volume, but only about one-third of the total number of cells in adult heart with the rest being a complex structure of connective tissue [58]. Extracellular matrix is composed of collagen, elastin bundles, and interconnected basement membranes. This 3D structure orients cardiomyocytes and mechanically couples them to blood vessels and nerve fibers. mRNA levels for collagen type I and cytoskeletal actin levels are significantly higher in the female heart as compared with the age-matched male heart in rat [59]. In humans, collagen type I, III, and IV are higher in adult males, while with aging (after 50), these proteins were higher in females [60]. This dimorphism is likely to contribute to the sex differences in heart remodeling.

Remodeling

Physiological and pathological conditions (exercise, pregnancy, heart abnormalities that cause heart to work harder, hypertension, etc.) may lead to heart tissue remodeling. Heart responds to myocardial wall stress by adding new sarcomeres in parallel to existing sarcomeres, increasing heart wall thickness (concentric hypertrophy). New sarcomeres can be added in series to existing sarcomeres (eccentric hypertrophy) characterized by dilation of the left ventricle without changes of the chamber wall thickness, observed, i.e., after endurance training. There is some evidence that with age the decrease in the total number of cardiomyocytes due to apoptosis is more prevalent in males compared to females, consistent with age-related decrease in left ventricle mass in men, but not women [58,61]. Worse diastolic and longitudinal function with advanced age or elevated load appears in both sexes, but a significant increase of torsion is more pronounced in women [62]. Ventricular cardiomyocyte numbers decline with age and this may be more prominent in men than in women; ventricular cardiomyocyte volume increases with age and this may be more pronounced in men than in women [63].

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Chapter 5

Cardiac conduction system

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Ever since the first description of sex-related electrocardiographic differences was made by Bazett [1] in 1920, a substantial number of animal and human studies exploring the underlying mechanisms has revealed their multifactorial genesis.

According to the currently available scientific data, all differences in the cardiac conduction system (CCS) between male and female hearts are based on a combination of the following factors:

I. Differences in anatomical structure.
II. Differences in the influence of autonomic and hormonal status on conduction tissue properties in addition to varying hormonal effects on autonomic tone and gene transcription.
III. Differences in gene expression, number, structure, and function of ion channels/transporter subunits, connexins (Cxs), and Ca^{2+}-handling proteins.

To better understand the origin of sex-related differences in the CCS, a short overview of the most frequently applicable research tools and techniques is helpful.

Methods of investigation

Clinical studies and electrophysiological testing

The most frequently and widely applied method for investigating the human CCS in a clinical setting is an electrophysiology study (EPS) that uses various modern mapping and navigation technologies. Testing of pharmacological and/or hormonal effects on cardiac conduction is often an integral part of a conventional EPS. Moreover, a double autonomic blockade allows to assess the influence of the autonomic nerve system on conduction parameters in male and female individuals.

Studies of cardiac tissue properties on isolated cells/tissues and whole heart models [2]

Analyses of cell culture systems (adult cardiac cells, cultured cell lines, embryonic stem cell−derived cardiomyocytes) and isolated cardiac tissue are widely used for modeling and studying electrophysiological tissue properties. Isolated tissues and heart models help us explore conduction properties and responses to pharmacological, hormonal, mechanical, and electrical effects.

Animal studies

The lack of information about intersystem interactions in isolated models can be overcome by investigating animal models in their entirety. Whereas large animal models are anatomically and physiologically more proximal to humans, small animal models are more amenable to genetic manipulations. Genetically altered animals are essential to reproduce the phenotype of human electrophysiological disorders once the genes responsible are identified.

Nonetheless, animal data should be carefully extrapolated to human electrophysiology due to existing differences between the animal species and humans.

Studies of cell electrophysiology

Studying cell electrophysiology with patch clamps is considered to be the "gold standard" for measuring membrane currents and characterizing ion channels without penetrating the cell membrane. For more selective measurements of the ion channels of interest, ion-selective microelectrodes (with liquid ion−exchange membranes in their tips) are used.

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Another modern research tool, optical mapping, enables the investigation of changes in intracellular Ca^{2+} content, pH, or other ions in addition to changes in transmembrane potential. This method is based on the assessment of changes in the quantity of emitted fluorescent light proportional to changes in transmembrane voltage or ionic concentration, depending on the actual research goal. With optical mapping, the electrical and mechanical activity of myocardial tissue can be simultaneously studied in a relatively undisturbed environment.

Investigation of gene transcription and protein expression for cardiac ion channels, transporter subunits, and gap junctions

Ion channels are fundamental determinants of the cardiac electrical activity, while connexins are crucial for cell-to-cell conduction. Their assessment includes two steps: gene transcription measurement and protein detection.

In modern molecular biology, three main techniques are applied to detect and quantify gene transcription: fluorescent in situ hybridization (FISH), quantitative polymerase chain reaction (qPCR), and, more recently, next-generation RNA sequencing (RNA-seq).

As the further translation of mRNA might be prevented by posttranscriptional regulation, it is reasonable to test for the presence of protein. This is commonly achieved by means of a western blot or immunohistochemistry study (the latter is more favorable for evaluating the location of the target protein in the cell).

Simulation using computational models

With ongoing technological progress, computer modeling and simulation have become a fundamental tool to study, predict, and optimize electrical behaviors and phenomena that cannot be measured directly. They are essential to generate and test hypotheses.

Sex-related differences at the atrial level

Sinoatrial node

Women are known to have a higher heart rate (HR), mainly due to the greater sinoatrial node (SAN) automaticity and shorter sinus node recovery time (SNRT) [3–9]. The average HR in women is one to eight beats (depending on the age group) higher than that of men [8,10].

Sex-related differences in HR and SNRT emerge early in life in school age children and continue into adulthood [9,11]. HR differences between the sexes persist after double autonomic blockade [6,12], so that they are thought to be related to the intrinsic differences in sinus node properties between the sexes.

A number of studies reported on the substantial sex-related differences in autonomic regulation of the heart. According to a metaanalysis on HR variability, women show a relative dominance of vagal activity despite their greater HR [13]. Possible explanations for that range from hormonal influences on the autonomic nervous system to sex-related differences in brain perfusion and in activities of certain brain structures such as the amygdala.

Direct and indirect hormonal effects on the SAN constitute another potential mechanism for sex-related differences in the SAN function. Clinical observations demonstrate a predominant occurrence (approximately 90%) of inappropriate sinus tachycardia in young women [14]. Women have faster HRs during the luteal phase of their menstrual cycle and during pregnancy [6,15,16].

From a molecular point of view, the human SAN is characterized by a high expression of the CaV1.3 L-type calcium channels and the CaV3.1 T-type calcium channels, as well as HCN1 and HCN4 isoforms (contribute to the I_f current, essential for the early diastolic depolarization of SAN cells) at both the mRNA and protein levels [17]. The autonomic nervous system controls HR through the regulation of the HCN channels. To achieve this, β-adrenergic agonists increase the levels of cAMP which positively shifts the I_f activation curve and increases its current density.

At present, no human data exist that look at the ion-channel expression profile differences in the SAN and hormonal effects on gene expression between the sexes.

Disruption of the gene coding for CaV3.1 T-type calcium channels abolished the T-type Ca^{2+} current ($I_{Ca,T}$), important in the initiation of action potential, in isolated mice cells from the SAN and atrioventricular node (AVN), and caused both sinus bradycardia and a slowing of the AV conduction without affecting the excitability of the right atrium [18].

Animal studies offer some insight into the hormonal effects on HR at the cellular level. The SAN cells of pregnant mice showed significantly faster HRs measured in the perfused isolated hearts (in the absence of autonomic regulation) compared with the nonpregnant mice [19]. The increased HR in pregnant mice was not secondary to changes in catecholamine level, intracellular concentration of cAMP, or the reduction of blood pressure. The authors found a significant increase in I_f density and an increased expression of HCN2 protein. One further study, conducted by the same research group, revealed increased L-type Ca^{2+} current ($I_{Ca,L}$) and CaV1.3 mRNA expression, along with a higher mRNA expression of ryanodine receptor (RyR), responsible for Ca^{2+} release from intracellular stores, in the SAN cells as an additional mechanism

for the increased automaticity in pregnant mice [20]. A schematic illustration of Ca^{2+} fluxes in cardiomyocytes is shown in Fig. 5.1 [21].

Furthermore, a long-term administration of 17β-estradiol to nodal-like human-induced pluripotent stem cell–derived cardiomyocytes (nodal-hiPSC-CM) accelerated cardiac automaticity, thus recapitulating the pregnancy phenotype in human SAN cell models (Fig. 5.2) [20].

In disagreement with these findings, other data from animal studies on isolated tissues demonstrated the negative chronotropic effect of 17β-estradiol on HR. Both acute nongenomic and long-term genomic effects are reported. A model of estrogen action in the cardiomyocyte is depicted in Fig. 5.3 [22].

The exposure of rat atria to 17β-estradiol was associated with an immediate dose-dependent decrease in sinoatrial

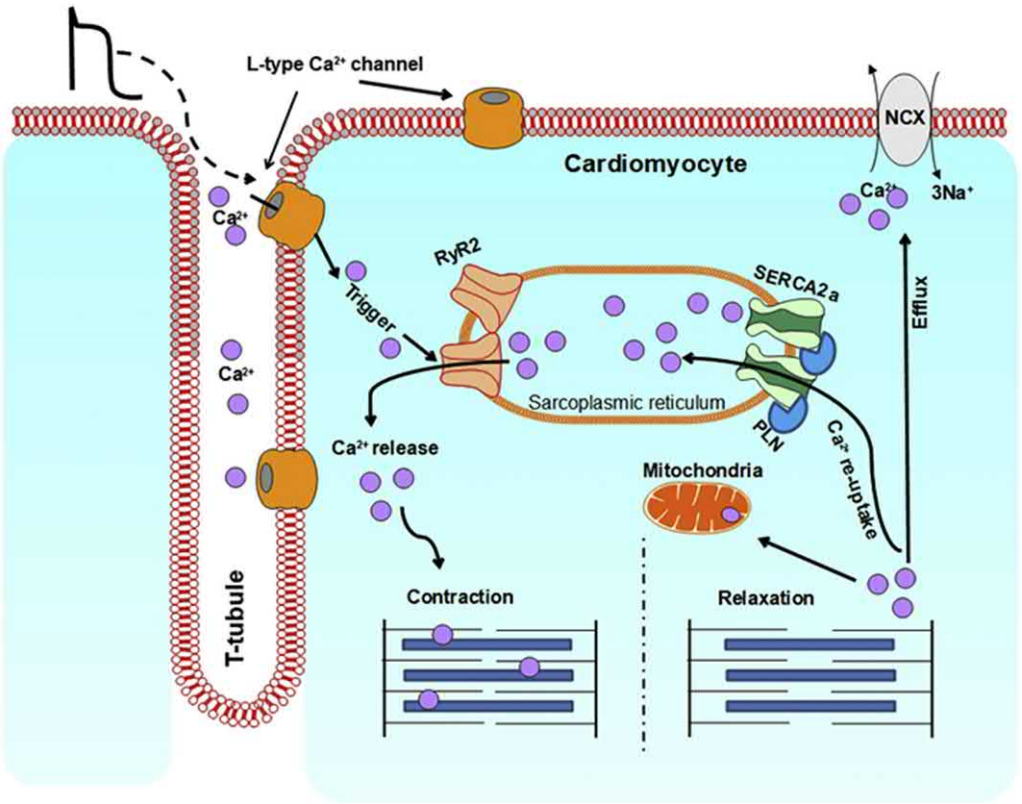

FIGURE 5.1 Intracellular Ca^{2+} fluxes during excitation–contraction in ventricular cardiomyocytes. *Reprinted from Mahmoodzadeh S, Dworatzek E. The role of 17β-estradiol and estrogen receptors in regulation of Ca^{2+} channels and mitochondrial function in cardiomyocytes. Front Endocrinol May 15, 2019;10:1–15 310. Copyright (2019) with permission from the authors.*

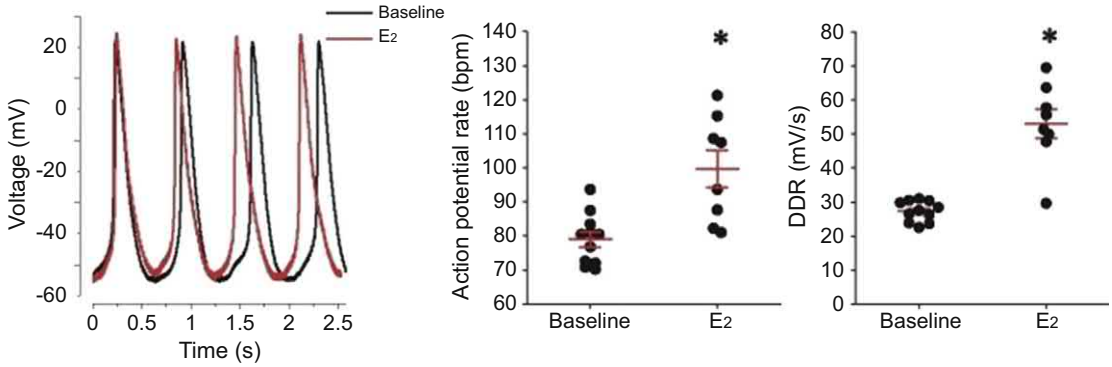

FIGURE 5.2 Effects of estrogen treatment (48–72 h) on action potential rate and diastolic depolarization rate (DDR). Typical spontaneous action potential obtained from nodal-hiPSC-CM with (red) or without (black) estrogen. *Reprinted from El Khoury N, Ross JL, Long V, Thibault S, Ethier N, Fiset C. Pregnancy and oestrogen regulate sinoatrial node calcium homeostasis and accelerate pacemaking. Cardiovasc Res October 1, 2018;114(12):1605–16. Copyright (2018), with permission from Oxford University Press.*

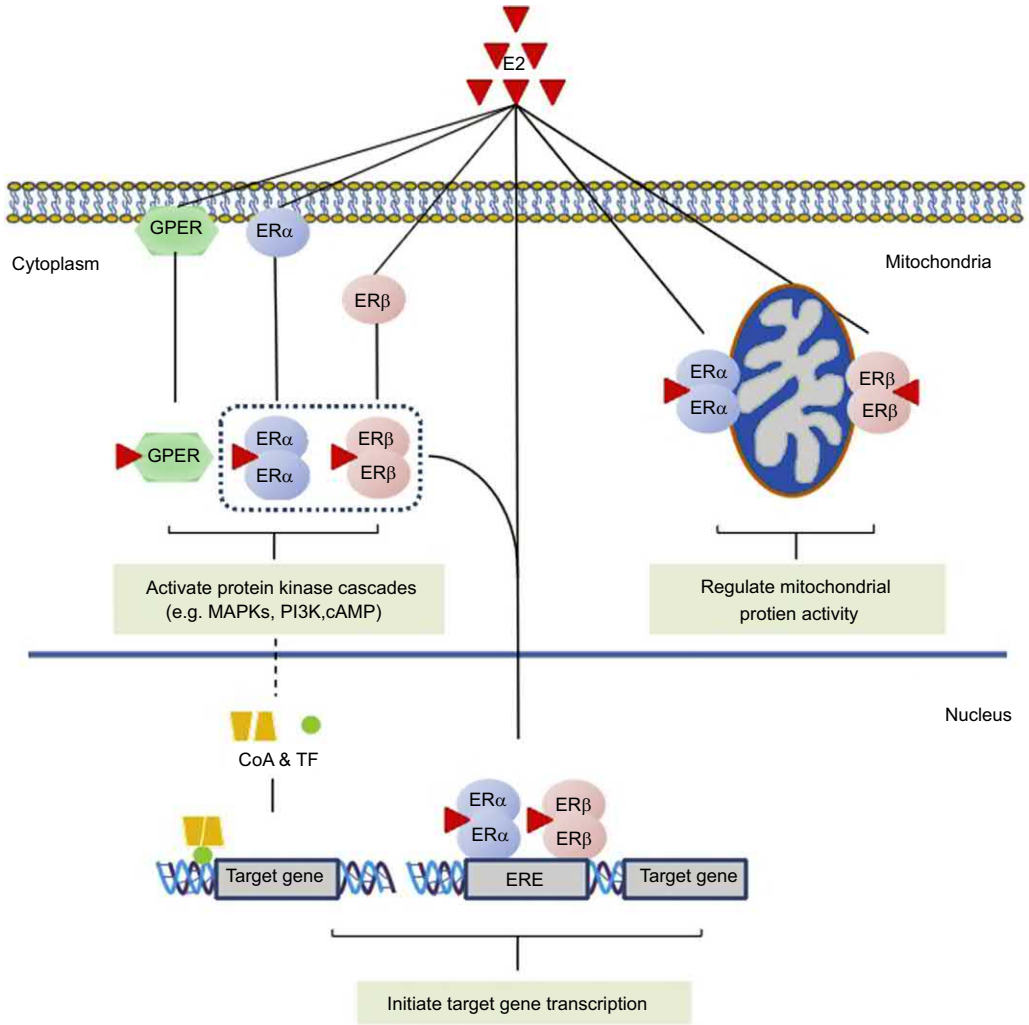

FIGURE 5.3 Estrogen (E2) action in the cardiomyocyte. Nongenomic effects are mediated through cytosol estrogen receptors, genomic effects are mediated through nuclear estrogen receptors. *Reprinted from Luo T, Kim JK. The role of estrogen and estrogen receptors on cardiomyocytes: an overview. Can J Cardiol August 2016;32(8):1017–25. Copyright (2006), with permission from Elsevier.*

rate [23]. In another study, long-term treatment with 17β-estradiol in physiological concentrations suppressed the activity of T-type calcium currents and significantly reduced HR in ovariectomized rats [24].

In dogs both estrogen and testosterone had similar effects on HR and on atrioventricular conduction times [25]. Castration of male as well as female dogs led to a slowing of HR and a significant prolongation of PQ intervals in both sexes. An inverted hormonal substitution restored the HR and PQ intervals to their initial values.

One postmortem study in Thai individuals found a decreased phosphorus content in the SAN of male individuals as they age compared with female individuals. As phosphorus is an essential part of DNA, RNA, and membranes, its decrease suggests a more marked reduction in the active cell density of the male SAN [26]. Though the data from German and Swedish pacemaker registers demonstrate that among adults >18 years old, men are less often affected by sick sinus syndrome and more often by atrioventricular block than women [27,28].

Atrial myocardium

Women demonstrate a faster impulse propagation throughout the atria expressed as a shorter P-wave duration as well as shorter PH and PR intervals compared to men in all age groups [5,29–31]. Sex-related differences in P-wave duration and PR interval seem to progressively increase with advancing age [5,32] except one study, where P-wave duration was found not to be age-dependent [29].

According to some observations, women have a shorter atrial effective refractory period (AERP) [9,33–35], whereas other investigations did not find any sex-related differences in AERP [3,36].

Although a shorter AERP was found in girls compared with age-matched boys [9], various studies support the impact of female hormones on AERP. The mean AERP during SR in premenopausal women was shown to be shorter than that in postmenopausal women and in age-matched men [34]. The degree of the shortening during atrial pacing and simultaneous AV pacing was significantly smaller in premenopausal women compared to postmenopausal women and age-matched men. In contrast, no changes in AERP in response to tachycardia were found between young (36 ± 16 years) and elderly men (60 ± 9 years) supporting the idea that the AERP differences may be hormone-driven and not age-related.

Contradictory data exist regarding the estrogen influence on atrial conduction properties. Experimental studies showed that 17β-estradiol shortened action potential duration (APD) in atrial myocytes without significantly affecting the resting membrane potential [37,38]. In both animal and human studies, 17β-estradiol suppressed the $I_{Ca,L}$ in atrial myocytes from female guinea pig hearts and in human atrial cardiomyocytes [38,39]. It could partly explain the shorter AERP in premenopausal women through the reduction in the plateau phase of atrial APD, which is mainly determined by $I_{Ca,L}$. Other studies provided different results. An acute administration of 17β-estradiol in menopausal women (who were previously ablated due to supraventricular tachycardia) significantly increased PA and AH intervals and prolonged AERP [40]. Similarly, a prolongation of atrial refractoriness in response to 17β-estradiol administration (although in supraphysiologic doses) was seen in ovariectomized dogs [41].

Despite the described dissimilarities in hormonal effects on atrial conduction, female hormones are consistently demonstrated to attenuate the shortening of AERP in response to tachycardia. Attenuation of the shortening in AERP is probably associated with the $I_{Ca,L}$ blocking properties of estradiol similar to verapamil [42].

Atrioventricular node

To date, there appear to be controversial data in regard to the presence and the extent of sex-related differences in AVN properties. Some studies reported significant variability in electrophysiological properties of the AVN between males and females [30,33,35,43], whereas other investigators found little or no differences in AVN physiology [3,4,44].

The most relevant clinical studies investigating AVN conduction properties are reviewed in Table 5.1.

When differences in AVN physiology between the sexes are observed, they are relatively consistent across all studies. Women have shorter PR, AH, and HV intervals, AVN-ERP, AV block Wenckebach cycle length (WbCL), and ERP of the slow pathway (SP-ERP). They demonstrate a shorter VA block WbCL and a lower incidence of baseline VA dissociation than men [30,33]. The combination of the shorter anterograde AV block WbCL (or SP-ERP) and the better VA conduction in women may partly explain their predominance in AVNRT occurrence. In turn, a longer AVN conduction time, which is required for manifestation of preexcitation, can be in part responsible for male predominance among patients with AVRT.

Autonomic tone inhibition shortens the AH interval and AVN-ERP significantly more distinctly in women than in men, even in the absence of any differences at baseline [12]. Mental stress caused similar changes, with a more pronounced shortening of AERP and AVN-ERP in women compared to men.

Clinical data demonstrate an impact of ovarian hormones on conduction characteristics of the AVN. Thus, despite the similar incidence of dual AVN physiology in men and women [30,33], AVNRT occurs up to 2 times more frequently in women [43,45], and this female preponderance is not observed in children <16 years [46]. The number and duration of SVT episodes correlate positively with plasma progesterone levels and negatively with 17β-estradiol levels [47]. Approximately 40% of female patients demonstrate perimenstrual clustering of SVTs with a better tachycardia inducibility at the time of low estrogen levels [48]. Women of premenopausal age (<50 years) have a significantly shorter AH interval, AERP, anterograde SP-ERP, and retrograde SP-ERP than women >50 years [33]. Premenopausal women also have a significantly higher incidence of anterograde multiple jumps and retrograde jump phenomenon than those of >50 years. Moreover, induction of AVNRT in men and women >50 years requires pharmacological substances (isoproterenol and/or atropine) more often in addition to pacing maneuvers than in the younger women. These observations could be also explained by the hormone-dependent augmentation of sympathetic activity. Estrogens are known to inhibit epinephrine release so that the hypoestrogenic states are usually accompanied by increased catecholamine levels [49,50]. Approximately 40% of female patients demonstrate perimenstrual clustering of SVTs with a better tachycardia inducibility at the time of low estrogen levels [48].

In contrast, men have up to twice the incidence of Wolff–Parkinson–White (WPW) syndrome as well as

TABLE 5.1 Clinical studies investigating electrophysiological properties of the atrioventricular node (AVN).

Study (defined by first author)	Number of patients	Sex	Parameters									
			PR	AH	HV	AERP	AVN-ERP	Anterograde WbCL	SP-ERP	FP-ERP	VERP	Retrograde WbCL
Kadish et al. [4] patients with SVT and indication for EP without structural heart disease	100	♀	Similar	Similar	Similar	–	–	Similar	–	–	Similar	–
		♂	Similar	Similar	Similar	–	–	Similar	–	–	Similar	–
Williamsson et al. [44] patients with AVNRT	141	♀	–	Similar	–	–	Similar	Similar	–	–	–	Similar
		♂		Similar			Similar	Similar				Similar
Taneja et al. [3] patients with paroxysmal SVT, syncope, nonsustained VT, palpitations, wide-complex tachycardia without structural heart disease	354	♀	Similar	Similar	**Shorter**	Similar	Similar	Similar	–	–	Similar	Similar
		♂	Similar	Similar	**Longer**	Similar	Similar	Similar			Similar	Similar
Liu et al. [30] patients with atrial tachycardia, syncope, idiopathic VT, palpitations without structural heart disease	96	♀	**Shorter**	**Shorter**	**Shorter**	–	**Shorter**	**Shorter**	Similar	Similar	–	Similar
		♂	**Longer**	**Longer**	**Longer**		**Longer**	**Longer**	Similar	Similar		Similar
Liuba et al. [43] patients with AVNRT, independent of the presence or absence of structural heart disease	203	♀	–	Similar	**Shorter**	–	**Shorter**	**Shorter**[a]	**Shorter**	Similar	–	Similar
		♂		Similar	**Longer**		**Longer**	**Longer**	**Longer**	Similar		Similar
Suenari et al. [33] patients with AVNRT	2088	♀	–	**Shorter**	–	**Shorter**	–	–	**Shorter (anterograde; retrograde**[b]**)**	**Shorter (anterograde)**	**Longer**	**Shorter**
		♂	–	**Longer**	–	**Longer**	–	–	**Longer**	**Longer**	**Shorter**	**Longer**
Huang et al. [35] patients with accessory atrioventricular pathways	1821	♀	–	Similar	–	**Shorter**	**Shorter**	–	–	–	**Longer**	–
		♂	–	Similar	–	**Longer**	**Longer**	–	–	–	**Shorter**	–

[a] *Only in women of childbearing age.*
[b] *Only in patients with atypical AVNRT.*

asymptomatic preexcitation [45,51–53]. Even so, in some studies male predominance was only observed in patients with WPW syndrome but not in those with concealed accessory pathways (APs) [35,46,54]. The male preponderance in AVRT is tendentially increasing in children as they age [46] which implies that sex hormones are involved. However, the relation of tachycardia manifestation to autonomic and hormonal status (e.g., perimenstrual association) is weaker in AVRT compared with AVNRT [48].

Men have more frequently antidromic AVRT; they demonstrate a shorter anterograde accessory pathway ERP (AP-ERP) than women with a higher prevalence of anterograde AP-ERP of <250 ms [35]. From an anatomical point of view, men have more left-sided pathways but fewer multiple pathways [35,51,55].

Sex-related differences at the ventricular level

A vast majority of available scientific data regarding the sex-related differences in human cardiac electrophysiology corresponds to the differences in ventricular repolarization. Women demonstrate longer QT and QTc intervals independent of the autonomic regulation and a higher occurrence rate of Torsade de pointes. Sex-related differences in repolarization are observed first at puberty with a progressive decrease in QTc duration in men, and they disappear with age (>50 years or even later) [56–58].

A shorter QTc in men relates to their shorter early repolarization phase of APD (J–T peak interval) compared to women. Simulation of testosterone's effects in humans shortened the cardiac cell APD mainly by the inhibition of $I_{Ca,L}$ responsible for early repolarization and less by the enhancement of the slow component of the delayed outward K^+ current (I_{ks}) [57].

In guinea pigs, testosterone was shown to rapidly shorten the ventricular APD in a dose-dependent manner, mainly due to the enhancement of the rapid component of the delayed outward K^+ current (I_{Kr}) and in part due to suppression of $I_{Ca,L}$ [59]. Moreover, in one other experimental study, testosterone was able to partially reduce a larger transmural dispersion of the depolarizing sodium currents (I_{Na}) found in the canine female ventricular myocytes [60].

The APD of female ventricular myocytes is longer than that of male cells in various animal and human models [61–64].

Canine female Purkinje fibers (PFs) exhibited a significantly longer APD at 50% (APD_{50}) and 90% (APD_{90}) of repolarization than male fibers [63]. In a condition mimicking bradycardia (stimulation rate of 0.2 Hz), even under normal K^+ concentrations, female PFs had a worse rate adaptation of action potential at APD_{90} (Fig. 5.4). In low K^+ conditions, female action potentials remained longer than male ones. Dofetilide, a highly selective I_{Kr}-blocker, in a bradycardia-mimicking condition provoked early

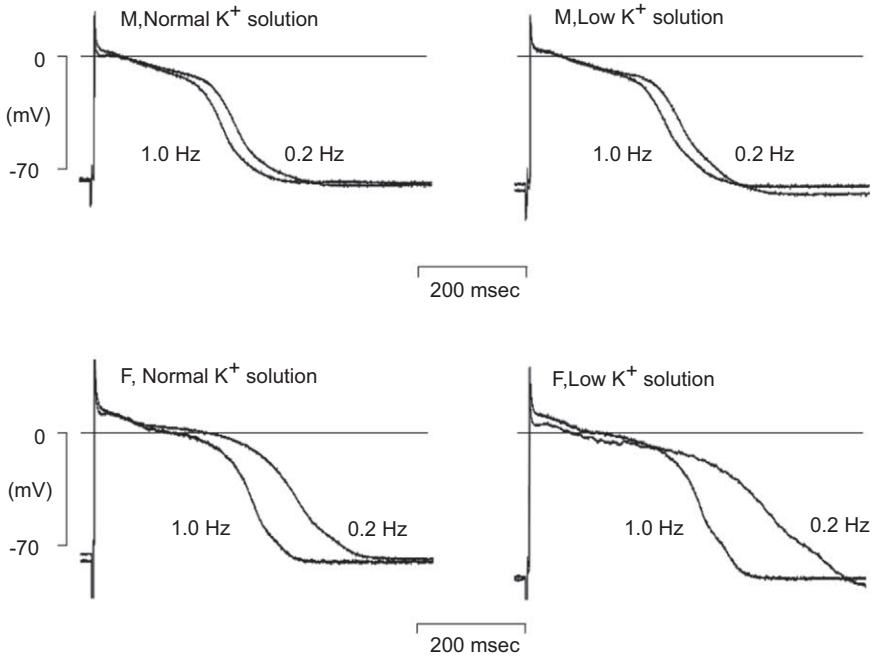

FIGURE 5.4 Effect of stimulation rate on APD_{90} in canine Purkinje fibers. Action potentials recorded in fibers from male (M) and female (F) animals under normal (left) and low (right) K^+ conditions. *Reprinted from Abi-Gerges N, Small BG, Lawrence CL, Hammond TG, Valentin JP, Pollard CE. Evidence for gender differences in electrophysiological properties of canine Purkinje fibres. Br J Pharmacol August 2004;142(8):1255–64. Copyright (2004), with permission from John Wiley and Sons Limited.*

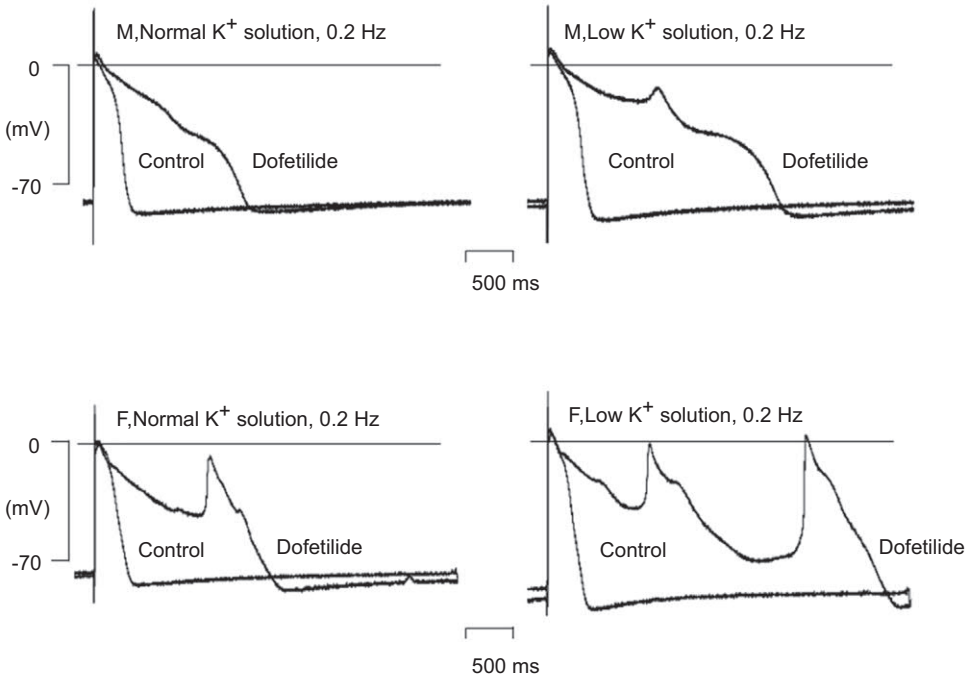

FIGURE 5.5 Early afterdepolarization activity in canine Purkinje fibers following I_{Kr} block. Action potentials recorded in fibers from male (M) and female (F) animals under normal (left) and low (right) K^+ conditions. *Reprinted from Abi-Gerges N, Small BG, Lawrence CL, Hammond TG, Valentin JP, Pollard CE. Evidence for gender differences in electrophysiological properties of canine Purkinje fibres. Br J Pharmacol August 2004;142(8):1255–64. Copyright (2004), with permission from John Wiley and Sons Limited.*

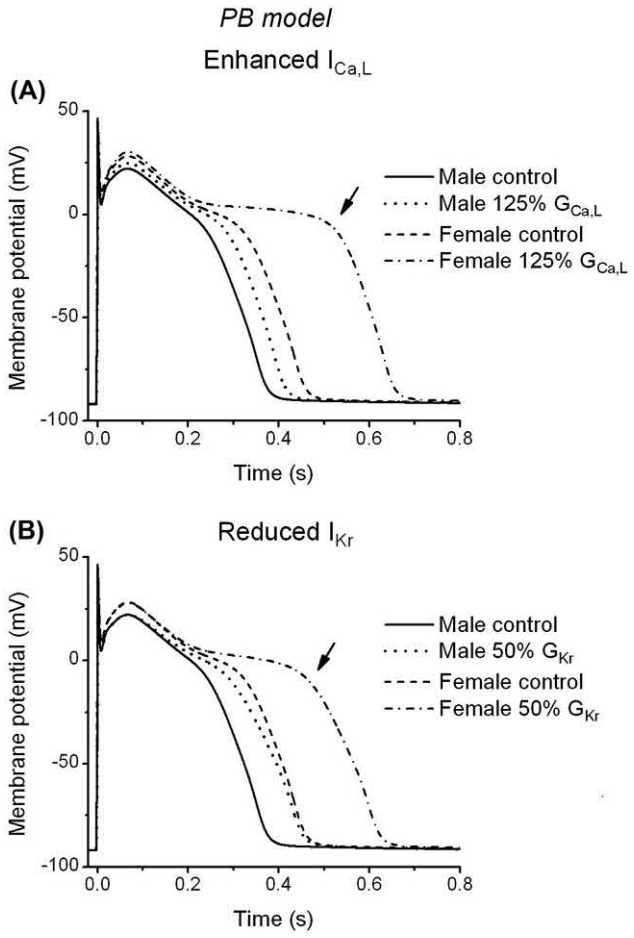

FIGURE 5.6 Superimposed action potentials of midmyocardial Priebe–Beuckelmann cells (0.1 Hz) with enhanced $I_{Ca,L}$ (A) or reduced I_{Kr} (B). Arrows indicate subthreshold "humps" in female cells. *Reprinted from Verkerk A, Wilders R, de Geringel W, Tan HL. Cellular basis of sex disparities in human cardiac electrophysiology. Acta Physiol.August 2006;187(4):459–77. Copyright (2006) with permission from John Wiley and Sons Limited.*

afterdepolarizations (EADs) and triggered activities with a significant higher incidence in female fibers (Fig. 5.5).

Mathematical modeling of human ventricular myocytes showed that female cells have a longer APD as well as a larger transmural APD heterogeneity than male cells [64]. Male cells showed more prominent phase-1 repolarization and were more susceptible to all-or-none repolarization. Simulations with 25% increased $I_{Ca,L}$ or 50% reduced I_{Kr} densities resulted in significant sex-related differences in action potential prolongation with subthreshold "humps" during phase-3 repolarization in females which implies their greater susceptibility to EADs (Fig. 5.6).

Human data from nondiseased donor hearts reported a lower expression of a variety of K^+-channel subunits in the female ventricles (HERG, minK, Kir2.3, Kv1.4, KChIP2, SUR2, and Kir6.2.1) and weaker repolarizing currents compared to male hearts [65]. Male hearts demonstrated a higher expression of Cx43 which is responsible for conduction velocity and abundantly present in the working myocardium.

Some experimental studies revealed a higher $I_{Ca,L}$ density in the female isolated ventricular myocytes compared to male cells [61,62]. In one other study, a greater dispersion in $I_{Ca,L}$ density was found only in castrated female rabbits treated either with 17β-estradiol or with 5-alpha dihydrotestosterone. The gonadal hormones had no effect on $I_{Ca,L}$ dispersion in castrated males [66].

In addition to the testosterone effect, experimental data report both acute and long-term effects of estradiol on APD.

Data from studies on isolated ventricular myocytes of guinea pigs and male rats indicated an acute prolonging effect of 17β-estradiol (in supraphysiologic concentration) on the ventricular APD by inhibiting both the I_{Kr} and the I_{Ks}, the transient outward current I_{to}, and reducing the inward $I_{Ca,L}$ [67,68].

Acute (nongenomic) modulation of ion currents by sex hormones (testosterone and estrogen) occurs via the MAPK signaling cascade or P13K-Akt-dependent activation of nitric oxide synthase (NOS) and NO release (Fig. 5.7) [69].

In cAMP-stimulated conditions, when I_{CaL} is enhanced by cAMP, sex hormones inhibit the activated $I_{Ca,L}$ (Fig. 5.8).

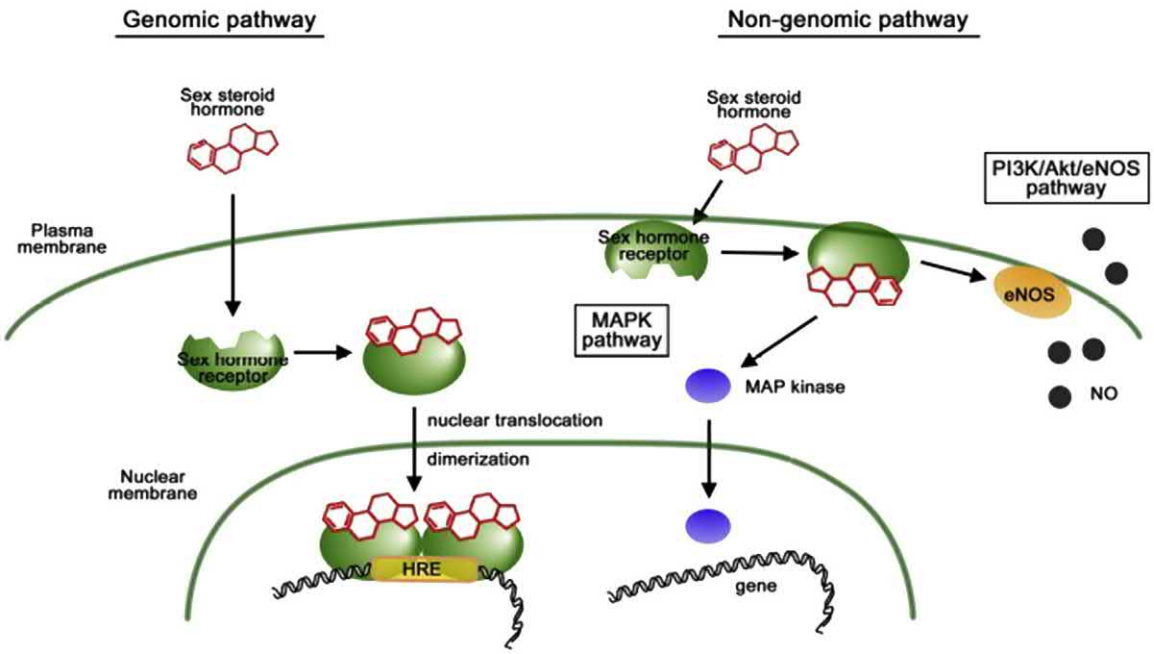

FIGURE 5.7 Genomic and nongenomic signaling pathways of sex steroid hormones. *Reprinted from Furukawa T, Kurokawa J. Regulation of cardiac ion channels via non-genomic action of sex steroid hormones: implication for the gender difference in cardiac arrhythmias. Pharmacol Ther July 2007;115(1):106−15. Copyright (2007), with permission from Elsevier.*

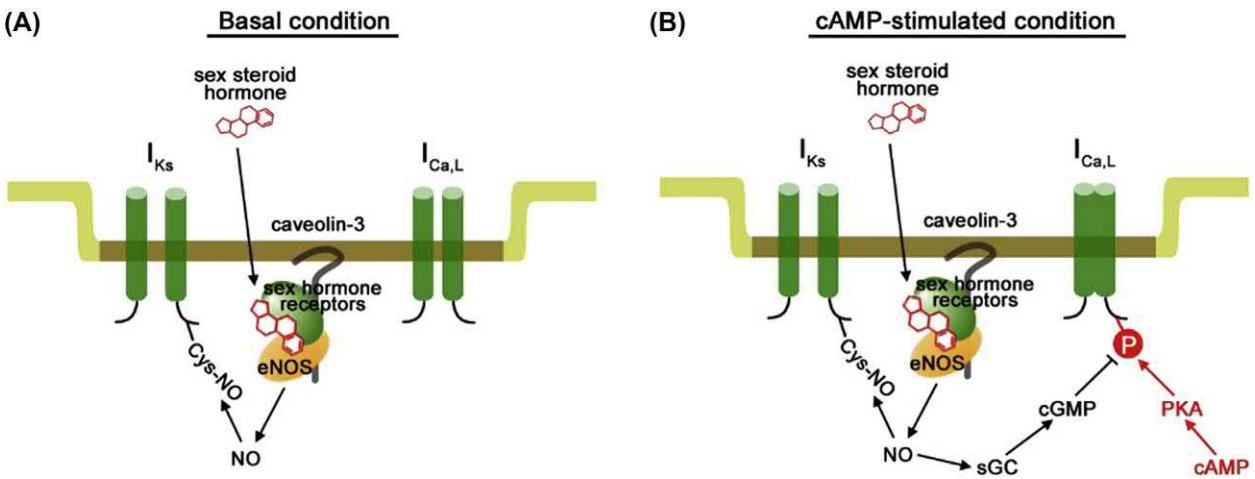

FIGURE 5.8 Rapid effects of sex hormones on I_{Ks} and $I_{Ca,L}$. Effects in the basal condition (A) and in the cAMP-stimulated condition (B). *Reprinted from Furukawa T, Kurokawa J. Regulation of cardiac ion channels via non-genomic action of sex steroid hormones: implication for the gender difference in cardiac arrhythmias. Pharmacol Ther July 2007;115(1):106−15. Copyright (2007), with permission from Elsevier.*

A high plasma estrogen concentration in mice was shown to be associated with a downregulation of Kv4.3 and Kv1.5 transcripts and a significant reduction in outward K^+ current (I_{to} and I_{Ks}) which resulted in APD and QTc prolongation [70].

In cardiomyocytes derived from human-induced pluripotent stem cells, estrogen was shown to upregulate $I_{Ca,L}$ and sodium−calcium exchange current (I_{NCX}) [71].

Women have a longer ventricular ERP (VERP) than men, and women >50 years have a significantly longer VERP than premenopausal women [12,33,35]. Inhibition of autonomic tone caused a more pronounced prolongation of VERP in women compared to men [12].

Men demonstrate a longer QRS duration as a result of their longer depolarization phase of APD compared to women [3,7,10,31,56,57]. Sex-related differences in QRS duration are likely to be independent of age [3,7,10,56,57] though some investigators found a narrowing of the QRS with the advancing of age in men compared to women [72]. By comparing QRS duration across different population groups, the sex-related differences in QRS duration diminished with increasing age in Chinese individuals but not in Caucasians [7].

Data from animal studies did not reveal any association between the QRS duration and hormonal status in dogs, indicating that the velocity of intraventricular conduction is apparently not overly affected by sex hormones [25].

To conclude, although sex-related differences in electrophysiological properties of the CCS are well recognized, there is a large number of conflicting data. The application of a combined investigative approach is the only way to improve our understanding of the underlying mechanisms that explain sex-related differences.

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Part III

Electrocardiography

Chapter 6

Morphology of normal resting electrocardiogram

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Introduction

There have been many publications on the normal limits of the conventional 12 lead electrocardiogram (ECG) and among the earliest of these is the classic treatise entitled "Differentiation between normal and abnormal in electrocardiography" by Ernst Simonson, published in 1961 [1]. This book is largely ignored in current literature, but even almost 60 years ago, it contained extensive descriptions on sex differences in the ECG, mainly relating to individual wave amplitudes, although sex differences in QRS duration and QT interval as well as QRS and T wave axes were also discussed. All measurements were made manually in those days, and it is interesting to look back and see how much was achieved around 1960 with manual methods. Nowadays, with larger databases stretching to millions of ECGs held on computer file, so much more data are available. Yet, it is probably fair to say that even those who are accustomed to interpreting ECGs on a daily basis would be stretched by having to set out normal limits of many of the ECG parameters of interest and then refine them on the basis of sex.

In 1975, Bourdillon et al. [2] wrote about the classification of the sex of subjects using the ECG. In an age-, race-, and weight-matched healthy population of 100 females and 98 males, these authors found that an equation using only five variables derived from an orthogonal lead system correctly classified sex in 82.3% of cases. A test set of 921 ECGs was correctly classified in 84.4% of cases. The authors' conclusion was that automated ECG analysis programs should take sex into account when interpreting an ECG.

By way of an introductory example, it is only necessary to consider leads V2 and V3 of the ECG to demonstrate sex-based differences. Fig. 6.1 shows V2 and V3 recorded from a healthy 29-year-old male and from a 28-year-old female.

It is immediately apparent that the ST amplitude is higher in the male ECG than in the female ECG. Indeed, from our own data on the normal limits of the ECG [3], it is found that the mean STj amplitude in V2 in males aged 18−29 years is 0.164 mV, while that for females in the same age range is 0.055 mV. In terms of the upper limits of normal, the corresponding values are 0.32 mV for males and 0.13 mV for females. Thus, the upper limit of normal ST amplitude in V2 in a female is even lower than the mean ST amplitude in a male.

Similar considerations apply in lead V3 where the upper limit of normal in females is 0.11 mV, which is approximately two-thirds of the mean amplitude in males, namely 0.15 mV.

It is probable that ST amplitude in V2 and V3 is the clearest differentiating factor between the normal male and female ECG. This feature applies throughout the adult age range. Differences in other measures are considered later.

In this chapter, which considers sex differences in the ECG, it goes without saying that the discussion resolves around the adult ECG. The pediatric ECG is significantly different from the adult ECG, particularly in the early days of life from when ECG morphology changes from being linked with a dominant right ventricle to a dominant left ventricle. Sex differences in QRS duration have been documented through our own work, even from the age of 1 [4], but these are not used in interpretation of the pediatric ECG. Indeed, they are rarely used in the interpretation of the adult ECG!

Much of the data in this chapter has been derived from a database of ECGs collected in the West of Scotland from apparently healthy individuals aged 18−82 years. Further details of the data collection can be found elsewhere [5].

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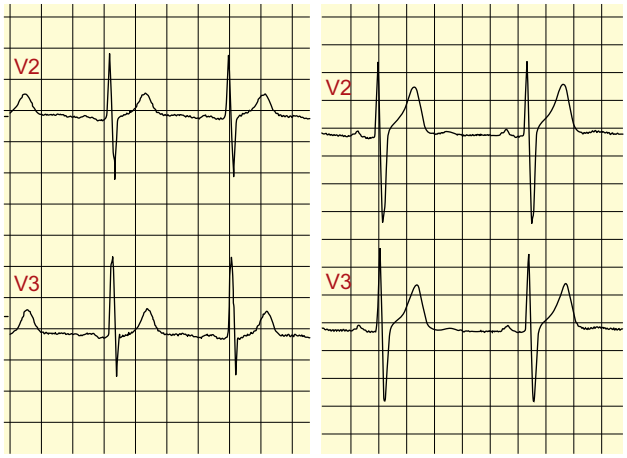

FIGURE 6.1 An illustration of appearances in V2 and V3 in a 20-year-old female on the left and from a 29-year-old male on the right. There is essentially no ST elevation at the onset of the ST segment in the female electrocardiogram (ECG) but clearly there is ST elevation in the male ECG.

Cardiac electrical activation

The electrophysiology of cardiac activation is relatively well known and is only sketched in outline here. Excitation normally begins at the sinoatrial node and the electrical impulse spreads through the atria giving rise to the P wave of the ECG. Activation reaches the atrioventricular node in the right atrium and then enters the Bundle of His. From there, it moves rapidly to the ventricles where activation proceeds via the specialized conducting system in the right and left ventricles and into the ventricular musculature.

Classically, the ventricular-specialized conducting system is regarded as splitting into two main branches, namely the right bundle branch and the left bundle branch. The latter was for many years regarded as dividing further into the left anterior fascicle and the left posterior fascicle. However, Demoulin and Kulbertus [6] showed that in many hearts there is a third fascicle central to the left and right fascicles (Fig. 6.2). More recently, others have elegantly published on what they have called the left septal fascicle and its relationship to left septal fascicular block [7]. They suggest that in 65% of hearts, there is a trifascicular left-sided conduction system, implying that only 35% of individuals have a bifascicular left ventricular conduction system.

The spread of excitation through the ventricles gives rise to the QRS complex of the ECG. Repolarization then takes place where the individual cardiac cells return to their resting state giving rise to the T wave on the ECG. Fig. 6.3 shows classical waveforms recorded in leads I and II, as

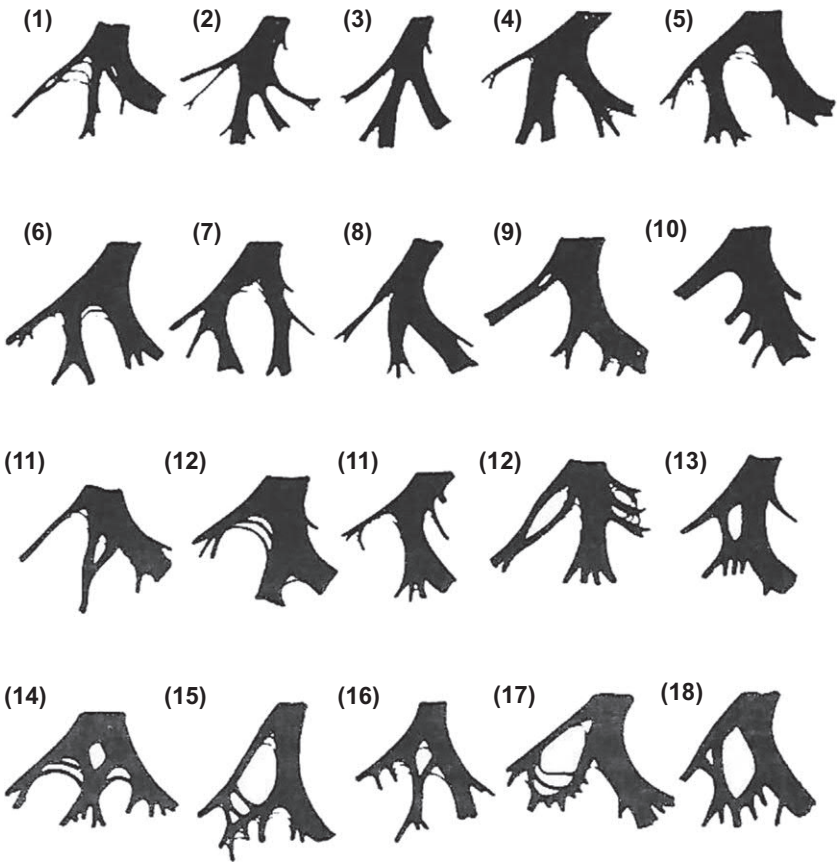

FIGURE 6.2 The trifascicular nature of the left ventricular conduction system in 20 individual hearts. *Reproduced with permission from Demoulin JC, Kulbertus HE. Histopathological examination of concept of left hemiblock. Brit Heart J 1972;34:807.*

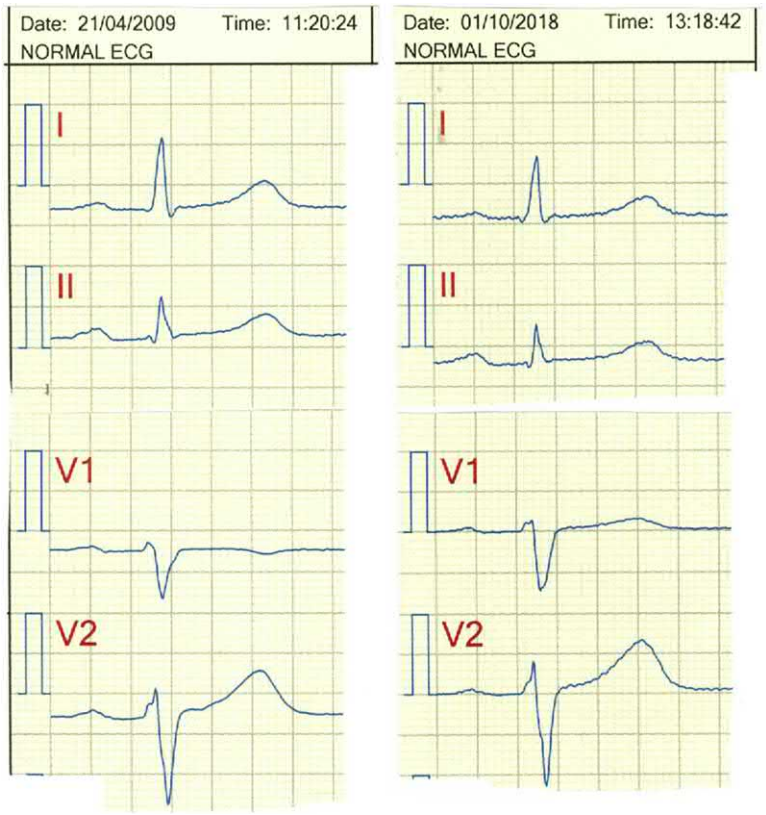

FIGURE 6.3 Appearances in leads I, II, as well as V1, V2 from a healthy 45-year-old male (left) and 9.5 years later (right). These two basic patterns are essentially repeated in different leads of the normal electrocardiogram. Note the T wave inversion in V1 in 2009 but an upright T in V1 in 2018. See text for further discussion.

well as in V1, V2. A fully detailed account of cardiac depolarization and repolarization can be found elsewhere [e.g., Ref. 8].

This author advises those learning the black art of ECG interpretation to begin by memorizing only the two different types of pattern which are seen in Fig. 6.3. By and large in the normal ECG, the pattern shown in leads I and II will be found also in aVL and aVF as well as in V5 and V6. The other pattern in V1 and V2 may be present in V3 but it will gradually transition to a lead I type pattern in leads V5 and V6. A full normal 12 lead ECG is shown in Fig. 6.4 where T wave inversion is apparent in V1. This a normal variant which is commonly seen in males but more so in females, while T wave inversion in V2 is rarely seen in healthy adult males but does occur in a small percentage of healthy adult females. T wave inversion is also apparent in lead III but this is also normal in view of the upright T in leads I and II. The beginner to ECG interpretation should largely ignore lead III when reporting an ECG as it may cause more confusion than assistance.

ECG wave durations

The P wave

The normal duration of the P wave is commonly regarded as being up to 120 ms but automated measurements tend to produce a slightly longer P wave duration giving an upper limit which is sometimes taken as 140 ms This is due to the fact that computer measurements tend to make use of all leads recorded simultaneously so that the P wave onset may be determined earlier in one lead compared to another. Consequently, the P wave termination may be measured later in some leads compared to others.

The author's own data [3] show that males have a mean P wave duration which is the order of 4 ms longer in males than females with a similar difference in the upper limit of normal.

Notwithstanding, recent publications on what has become known as Bayes syndrome [9], which is linked with inter atrial block, regard a P wave duration $\geq$ 120 ms as abnormal because the abnormality was initially characterized via manual measurement of P wave duration in individual leads. In practice, the diagnosis can still be made on the basis of an individual lead measurement of P wave duration which is often very difficult.

PR interval

The mean PR interval, according to the author's data (Table 6.1), has a duration of between 152 ms for males aged under 30 years and 161 ms for males $\geq$ 50 years. Corresponding figures for females are 146−156 ms. It can be seen that the mean PR interval is a little longer in men

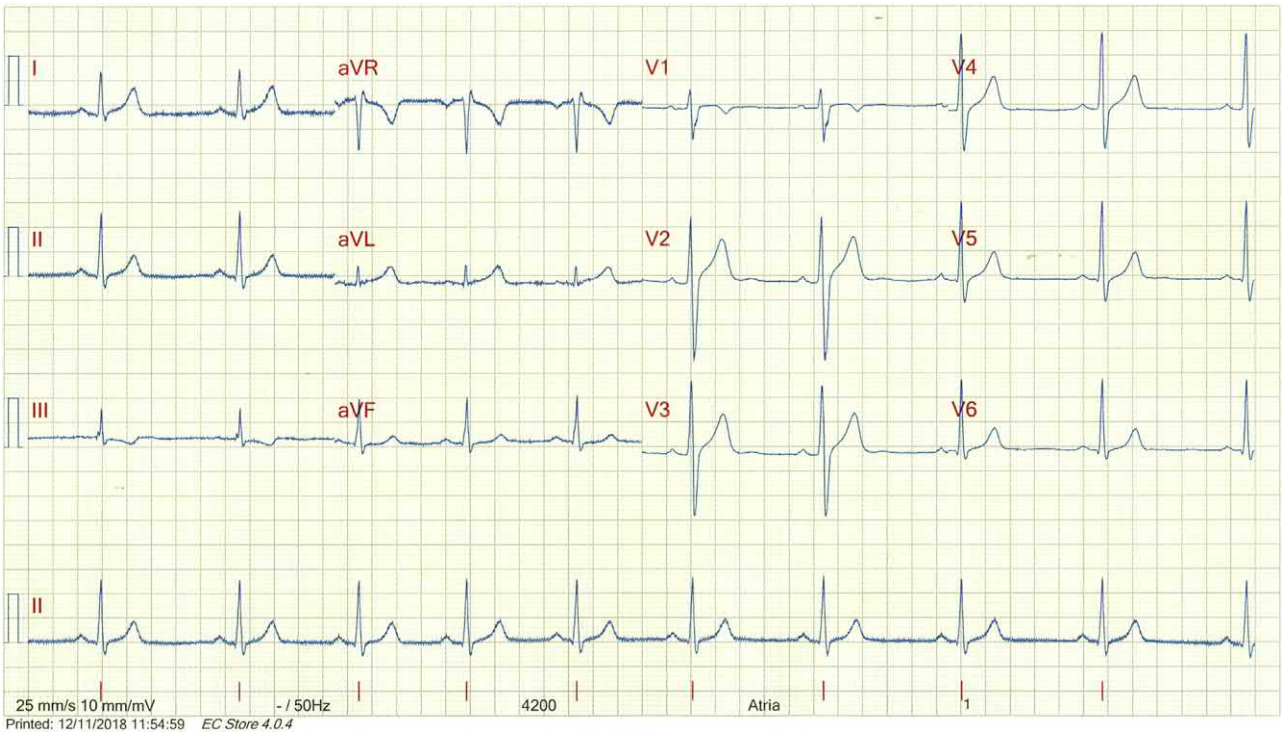

FIGURE 6.4 A normal 12 lead electrocardiogram (ECG) from a 29-year-old male. Note the T wave inversion in leads III and V1 in this normal ECG.

than in women but in general terms, diagnostic criteria for an abnormal PR interval do not make use of this small sex-based difference.

The above data also show that the PR interval lengthens with increasing age, but again, this is not generally recognized in diagnostic criteria. The upper limit of normal varies with sex and for females is 200 ms and for males is 210 ms based on data from the author's lab [3]. Some automated programs will regard borderline prolonged PR interval as between 200 and 220 ms and will not report first-degree AV block until the PR interval has exceeded 220 ms This is in order to maintain a high degree of specificity in reporting this abnormality.

QRS duration

The QRS duration has been known to be longer in males than females for many years—see Ref. [1], for example. In the Glasgow database of apparently healthy Caucasians, mean QRS duration in young males 18−29 years of age was 96.4 ms and in females 87.7 ms (Table 6.1). This difference was maintained through to those aged over 50 years where in males the mean QRS duration was 92.7 ms compared to 87.1 ms in females. The upper limit of normal was 114 ms in young males and 104 ms in young females, while it was 112 ms in older males and 104 ms in older females. Thus, there is a clear difference in the upper limit of normal QRS duration between the sexes though little difference with respect to age.

Notwithstanding the foregoing, there are few if any diagnostic criteria routinely used by cardiologists that differentiate between males and females with respect to interpretation of QRS duration. Commonly, left bundle branch block would be reported with a QRS duration $\geq$120 ms with no differentiation made between the sexes, as, for example, in the AHA/ACCF/HRS Recommendations of 2009 [10]. Strauss et al. notably incorporated a small difference between males and females in criteria for strict left bundle branch block, where the criterion for abnormal QRS duration is 140 ms for males and 130 ms for females [11].

It is worth noting, given the significance of QRS duration particularly in relation to some types of therapy such as for Cardiac Resynchronisation Therapy (CRT), that sex differences in QRS duration are maintained in different racial groups [12].

In relation to application of automated measurements for whatever reason, such as CRT, it should be noted that QRS duration is measured differently by bespoke software used by a variety of manufacturers of ECG machines, as confirmed in a recent study [13]. For example, one software package calculated the mean QRS duration in 423 women to be 80 ms, whereas on the same data, another package had a mean QRS of 91 ms in women. The same packages used for 377 males produced corresponding results of 90 and 95 ms. Hence, if critical decisions have to be made clinically in relation to QRS duration, manual

TABLE 6.1 Normal limits of P, QRS, and QTc duration in 1408 apparently healthy Caucasians [3].

	18–29 years		30–39 years		40–49 years		≥50 years	
	M	F	M	F	M	F	M	F
	n = 265	n = 317	n = 218	n = 215	n = 119	n = 72	n = 123	n = 79
P	152.5 ± 23.0	145.9 ± 19.7	155.7 ± 21.4	145.7 ± 18.6	157.2 ± 21.8	154.9 ± 20.4	161.5 ± 18.9	155.6 ± 6.9
QRS	96.4 ± 8.6	87.7 ± 7.8	95.4 ± 9.8	88.6 ± 7.3	94.4 ± 9.9	89.4 ± 7.9	92.7 ± 9.3	87.1 ± 8.7
QTcH	403.6 ± 19	411.6 ± 18	404.8 ± 19.4	415.2 ± 16.9	409.2 ± 17.9	415.2 ± 22.5	407.4 ± 17.5	419.5 ± 22.7
QTcB	413.9 ± 23.1	429.7 ± 22.9	416.0 ± 22.9	432.6 ± 20.9	420.0 ± 21.9	433.7 ± 28.4	420.9 ± 22.7	438.2 ± 24.8

QTcH is QT corrected according to the Hodges formula [15] and QTcB is QT corrected according to the Bazett formula [16].

measurements should be considered as a backup or second opinion in relation to any automated measurement.

QT interval

The QT interval is known to be marginally longer in females than males, as shown in a number of studies. The most recent guidelines suggest 450 ms as an upper limit of normal for males and 460 ms as an upper limit of normal for females if the QT interval is corrected on the basis of heart rate [14]. However, it must be noted that the corrected QT interval, denoted QTc, will have different values based on the correction method used.

The aim of QT correction is to estimate the QT interval in an individual at a heart rate of 60 beats/minute. There are several formulae available but the 2009 AHA/AFFC/HRS Recommendations suggested that a linear correction formula should be used [14]. An example is the Hodges formula [15].

$$\mathrm{QTc} = \mathrm{QT} + 1.75(\text{Heart Rate} - 60) \tag{6.1}$$

On the other hand, the nonlinear Bazett formula [16], namely

$$\mathrm{QTc} = \mathrm{QT}\sqrt{(\text{rate}/60)} \tag{6.2}$$

is still widely used. A full discussion on QT correction can be found elsewhere [17].

Normal QTc measurements from the author's database can be found in Table 6.1. It can be seen that the mean QTc interval in females is longer than the mean QTc in males. This difference is maintained through the different age ranges (Fig. 6.5). It should also be noted that the difference in mean QTc between females and males based on the Bazett formula is almost twice that based on the Hodges formula.

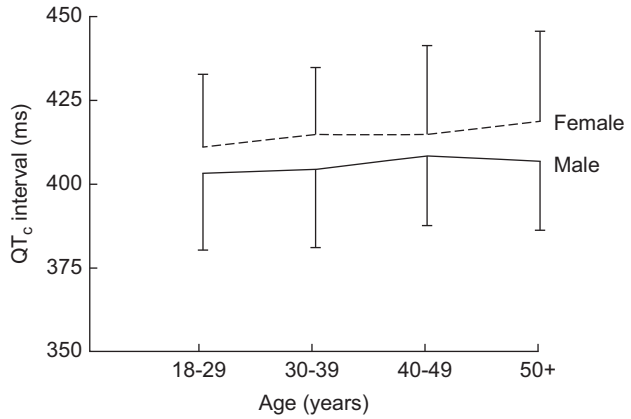

FIGURE 6.5 Mean and standard deviation of normal QTc intervals in 1408 Caucasian males and females [5]. The Hodges equation was used to correct the QT intervals [15].

The normal QT morphology is reflected in Figs. 6.2 and 6.3 where there is a high degree of symmetry within the T wave itself but little difference in shape of the male and female T wave. More asymmetrical patterns of QT can be found in the so-called long QT syndrome, but this is sometimes due to a lengthened ST segment.

It should be noted that automated programs vary in measuring any interval on an ECG [13], and it is difficult with a manual measurement to be more accurate than to 10 ms particularly in measuring QT interval.

ECG waveform amplitudes

P wave amplitudes

In the normal ECG, the P wave, which is due to atrial activation, is not regarded as having any sex-dependent morphology. The early part of the P wave is due to right atrial activation, and it is generally accepted that the terminal portion of the P wave is due in the main to left atrial activation. For this reason, the P wave in V1 may have a bifid morphology reflecting the posterolateral direction of activation in the left atrium.

The product of the terminal P wave duration and the terminal inverted portion of the P wave in V1 is sometimes called the P terminal force or the Morris Index [18] and is regarded as having an upper limit of normal of 40 ms × 0.1 mV, i.e., 4 ms mV.

QRS amplitudes

Perhaps one area of electrocardiography where there is least appreciation of sex differences in ECG morphology, when this should not be the case, is that of amplitudes of different components of the QRS complex. For example, perhaps the best known criterion for left ventricular hypertrophy (LVH) is the sum of the amplitudes SV1 and RV5. The original publication by Sokolow and Lyon in 1949 [19] suggested a single threshold of 3.5 mV for the upper limit of normal. This study was based on a relatively small number of individuals without the assistance of automated measurements of ECG amplitudes.

More recent studies using digital electrocardiography in larger databases show quite clearly that precordial lead amplitudes vary with the sex and age of an individual. Fig. 6.6 shows the upper limit of normal SV1 + RV5 for males and females of different ethnic groups [12]. From this it can be seen very clearly that, particularly in males, younger individuals have a higher voltage than older individuals. In addition, it can be seen that young males have much higher QRS amplitudes than young females.

More recently developed criteria such as the Cornell voltage [20] are sex dependent. This index is RaVL + SV3, with thresholds of 2.2 mV for females and 2.8 mV for

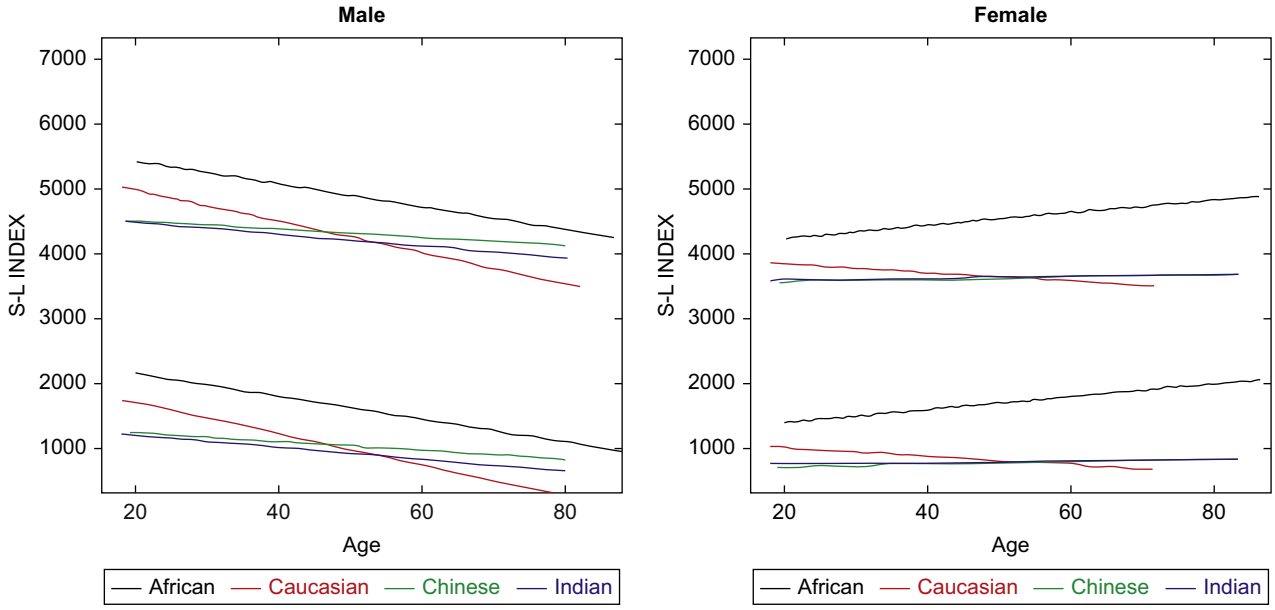

FIGURE 6.6 The upper and lower normal limits of the Sokolow and Lyon Index SV1 + RV5 in males and females. These limits were obtained from four different populations: Caucasian (Scottish), Black (Nigerian), Chinese (ROC), and South Asian (India). *Reproduced from Macfarlane PW, et al. Racial differences in the ECG — selected aspects. J Electrocardiol 2014;47(6):809–8014 with permission.*

males for a diagnosis of LVH. These criteria are not age dependent in complete contrast to those of Sokolow and Lyon as confirmed recently in a small study [21].

An understanding of the age–QRS voltage relationship has led to recent guidelines for abnormal ECGs in athletes to acknowledge that high QRS voltages in young fit individuals are not necessarily abnormal, particularly in the absence of accompanying T wave abnormalities [22].

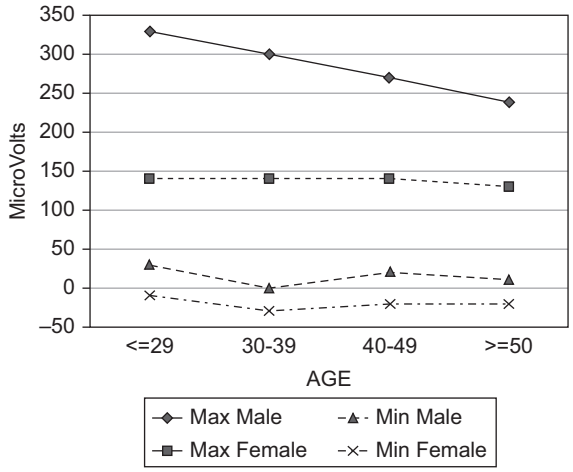

FIGURE 6.7 Upper and lower normal limits of ST amplitude in V2 for Caucasian males and females. *Reproduced from Macfarlane PW. Age, sex and the ST amplitude in health and disease. J Electrocardiol 2001;34:235–41 with permission.*

ST amplitude

Work particularly in the author's laboratory showed that the amplitude of the ST segment, e.g., at its onset (ST_j), was also age and sex dependent [23]. Fig. 6.7 shows the trend of the upper and lower normal limits of ST amplitude for healthy males and females in lead V2. It can be seen that the upper limit of normal ST_j is certainly age dependent in males but not in females. However, there is a substantial difference in the upper limit of normal between males and females, with males having over double the upper limit of normal amplitude in females in the younger ages up to 40 years. Similar amplitude differences can be seen in limb leads such as lead I (Fig. 6.8), although the differences are not so marked as in precordial leads, e.g., approximately 200 μV in the youngest age range for V2 versus 30 μV in lead I (Figs. 6.7 and 6.8).

Fig. 6.9 shows the upper normal limits of ST amplitude in all the precordial leads for males and females. It should be noted that the upper limit for V1 approximates that of V5 in males and initially appears to follow a similar trend in females but in later years this is not the case.

The slope of the ST segment is also sex dependent. Fig. 6.10 shows how the ST slope is steeper in males compared to females, and although the slope decreases a little with increasing age, the sex difference is maintained at all ages.

An understanding of these differences is important when considering diagnostic criteria for myocardial infarction. The most recent guidelines for ST Elevation Myocardial Infarction (STEMI) now have age- and

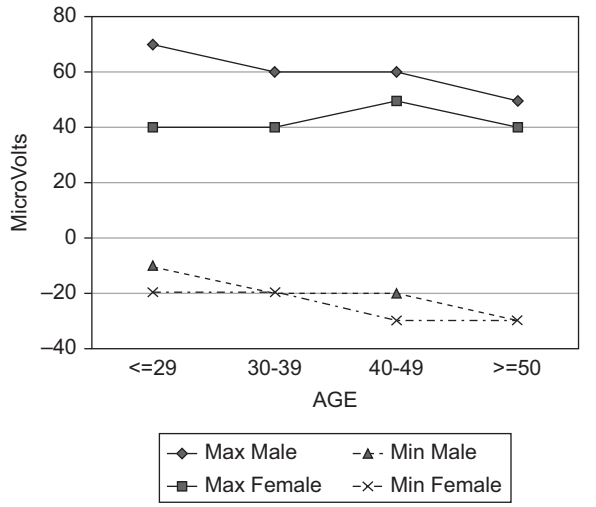

FIGURE 6.8 Upper and lower normal limits of ST amplitude in lead I for Caucasian males and females. *Reproduced from Macfarlane PW. Age, sex and the ST amplitude in health and disease. J Electrocardiol 2001;34:235–41 with permission.*

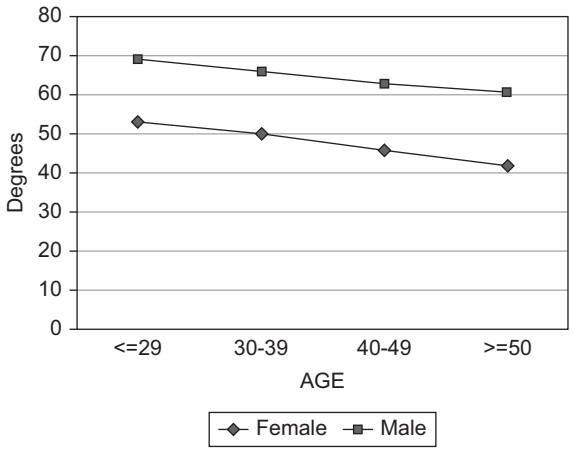

FIGURE 6.10 Upper limits of normal ST slope in V2 for Caucasian males and females. *Reproduced from Macfarlane PW. Age, sex and the ST amplitude in health and disease. J Electrocardiol 2001;34:235–41 with permission.*

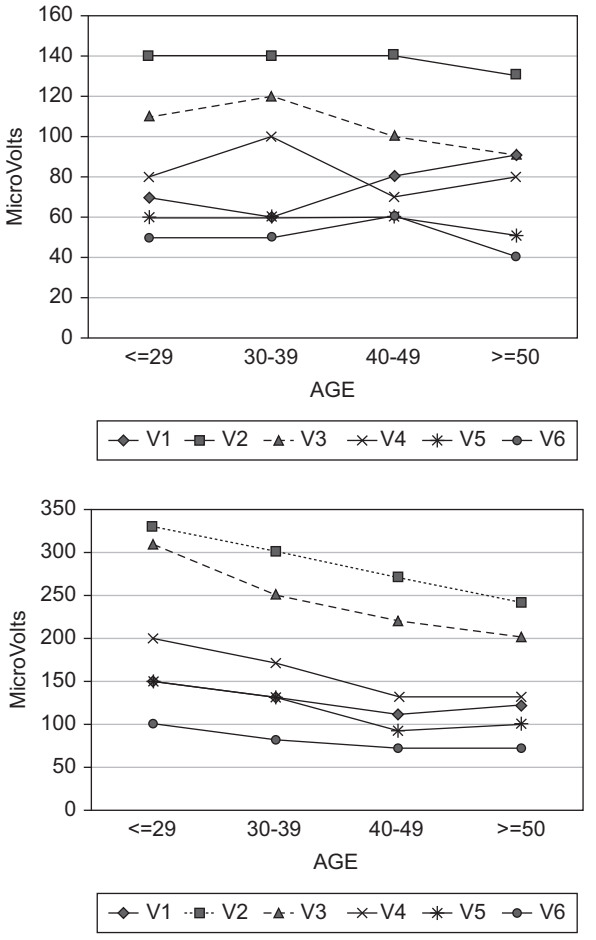

FIGURE 6.9 Upper limits of normal ST amplitude in V1 to V6 in Caucasian females (top) and males (bottom). Note the differing scales in the two graphs but similar sequences of maximum toward the minimum values across leads in each graph. *Reproduced from Macfarlane PW. Age, sex and the ST amplitude in health and disease. J Electrocardiol 2001;34:235–41 with permission.*

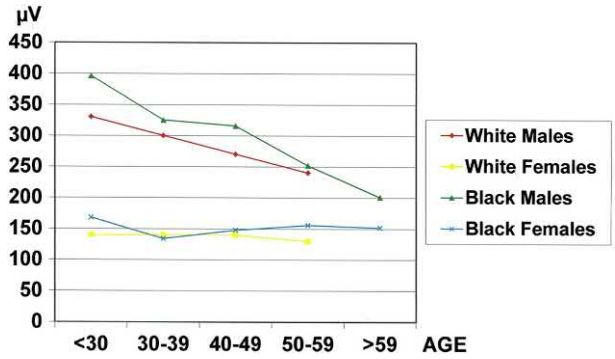

FIGURE 6.11 (Nigerians—green and blue, for males and females respectively) and Caucasians (red and yellow for males and females respectively).

sex-dependent thresholds for abnormal ST elevation [24]. A cardiologist reviewing an ECG from an individual with a suspected myocardial infarction is unlikely to be assessing tables of normal limits before making an interpretation but can be assisted by automated interpretation providing some guidance as to whether ST amplitudes are normal or abnormal. It is also difficult to remember normal limits of STj in V1–V6 which vary from lead to lead particularly in males in Fig. 6.9. There is also a sex-based difference in STj in all precordial leads (Fig. 6.9). Similar considerations apply in different races as illustrated for V2 in Fig. 6.11 for blacks living in Nigeria [25].

In general terms, with the exception of aVR, the ST segment is minimally elevated in all leads. As heart rate increases, there is a tendency for the ST segment to be a little depressed in the inferolateral leads.

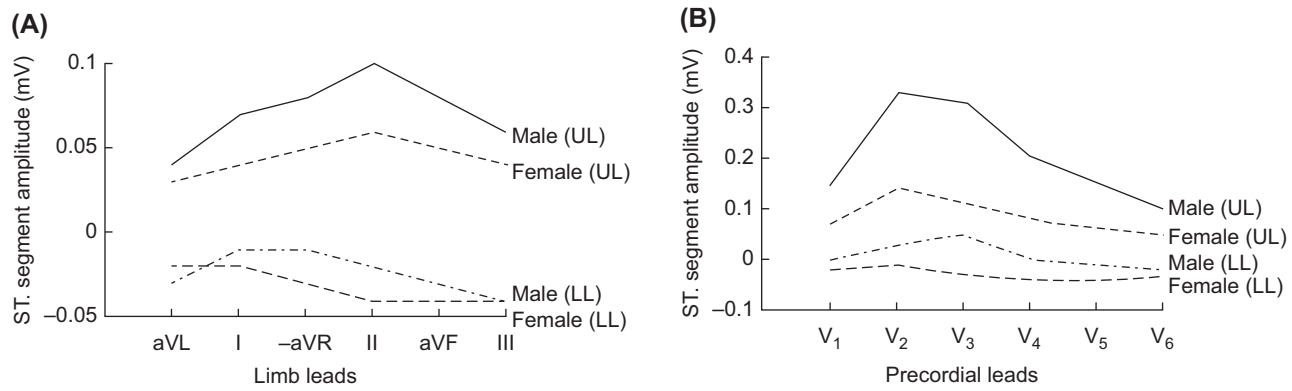

FIGURE 6.12 Upper and lower limits of T wave amplitude in (A) limb leads and (B) precordial leads recorded from healthy Caucasians aged over 18 years. *Reproduced from Macfarlane PW, Lawrie TDV. The normal electrocardiogram and vectorcardiogram. In: Macfarlane PW, et al, editors. Comprehensive Electrocardiology. London: Springer; 2011, vol. 2. p. 485–546 with permission.*

T wave amplitudes

The T wave, generated by recovery of the myocardium following ventricular depolarization, is a diagnostically important section of the ECG. In a classically normal ECG, the T wave will be upright in most leads with the exception of aVR and on occasions V1, and to a lesser extent V2, particularly in females. In a very small percentage of adults, there may be minimal T wave inversion in lead III corresponding to a normal T axis in the region of 0–20 degrees in the frontal plane. Similarly, a very small percentage of healthy individuals will have minimal T wave inversion in aVL corresponding to a T wave axis in the area of 60–90 degrees.

In the precordial leads, T wave inversion in V1 is much more frequent in females than males. In the Glasgow database [3], a negative T component was present in approximately 35% of males in the 18–29 age group compared to almost 70% of females in the same age group. In those aged over 50, corresponding figures were 15% for males and approximately 40% for females. In V2, T wave inversion was absent in young males and present in approximately 1% of young females. In the over 50 years age group, in V2, the prevalence of T wave inversion was 0.5% in males and 1% in females.

Sex differences in T wave amplitudes are present in both limb and precordial leads. Fig. 6.12 shows upper and lower limits for males and females in limb and precordial leads. In general terms, diagnostic criteria do not make much use of these differences, perhaps with the exception of consideration of hyperkalemia. In such cases where tall T waves may be found in precordial leads, an allowance should be made for the fact that women have lower normal limits of T wave amplitude than males. A typical criterion for hyperkalemia might be that the T wave amplitude in V3, V4, and V5 has to exceed 1.2 mV in each lead for abnormality in males, whereas in females, the threshold is 0.75 mV.

Conclusion

Overall, there are significant sex differences in ECG appearances between males and females, and those who are involved with ECG reporting are encouraged to familiarize themselves with such known findings.

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Chapter 7

Sex differences in QRS complex duration

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Sex differences in duration of the QRS complex on surface electrocardiogram (ECG) have long been recognized. Shorter QRS duration in females has been documented in a number of publications mostly dealing with cardiac resynchronization therapy in which the QRS duration plays a pivotal role [1−3]. Similar observations of the same sex difference have also been made in other patient populations including younger patients recovering from acute myocardial infarction [4], patients in needs of other cardiac electrical therapy [5], patients with idiopathic ventricular tachycardia originating from right ventricular outflow tract [6], with systolic heart failure [7], with left ventricular hypertrophy [8], with acromegaly [9], and many other populations of patients with well-defined clinical conditions.

Somewhat less numerous but still sufficiently systematic and convincing are reports based on investigations of healthy subjects, either based on population-wide studies [10], previous early pharmacology investigations [11], or focusing on electrocardiography in athletes [12]. All these publications also report shorter QRS complex in females.

Lesser attention has been paid to the dependency of QRS complex duration on the underlying heart rate. This has recently been the subject of two investigations in healthy subjects [13,14] which also addressed the differences between the sexes. While both studies fully agreed on the fact that females have shorter QRS duration than males, their other details (e.g., the profile of the heart rate dependency) did not fully agree, perhaps because of methodological differences including differences in the accuracy of electrocardiographic measurements [15,16].

In the light of these potential differences between previous reports, it is appropriate to review the previously analyzed data in more detail. Thus, this chapter recapitulates our previous data analyses [14] and, in addition the principal observations, presents a number of previously unpublished results.

Observations and data analyses

As previously published, the ECG data that we summarize here originated from two clinical pharmacology studies conducted in healthy subjects in whom repeated 12-lead day-time Holter recordings were made at baseline when the subjects were free of any treatment. All the subjects had normal screening ECG and normal clinical investigation usual in clinical pharmacology studies [17]. Both studies were approved by the relevant ethics boards and all participants gave written informed consent. Since only off-treatment data were analyzed, the details of the source studies are of no relevance.

Using previously described techniques [18,19], multiple ECG measurements were made in the day-time portions of the 12-lead Holter recording. The measurements utilized representative morphologies derived from 10-second portions of the source recordings and were sampled at 1000 Hz. QRS width was measured from the global QRS onset to the global QRS offset, i.e., from the earliest onset in any of the 12 leads to the latest offset in any of the 12 leads. Published pattern matching algorithms [20,21] were used ensuring that similar morphologies of the QRS onset and offset were measured consistently. All measurements were visually verified and manually corrected. The cardiologists verifying the measurements were blinded in respect of the characteristics of the study subjects including their sex, age, and race. Multiple measurements were made in each recording using ECG samples preceded by stable heart rates with nominal variations of up to 2 beats per minute (bpm) in the preceding 2 min. The measurements were made when the subjects were supine as well as during postural provocations and free daily activity. This led to substantial heart rate ranges in each subject [19].

Individually optimized linear regressions in the form $QRS = \beta + \alpha * RR$ and a log/log regression model in

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the form $\log(QRS) = \beta + \alpha * \log(RR)$, that is $QRS = \beta' * RR^{\alpha}$ (where both QRS duration and RR interval are in seconds, and $\beta' = e^{\beta}$), were obtained for each subject. To increase the precision of the heart rate dependency, curvilinear models [22] were also constructed in the form $QRS = \eta + \frac{\delta}{\gamma} * (RR^{\gamma} - 1)$, where η, δ, and γ are the central value, slope, and curvature of the curvilinear regression model, respectively. All the models were individually optimized in each subject to obtain the best fit between the RR interval durations of the underlying heart rate and the corresponding QRS duration. We have subsequently noticed (see further) that mathematically more accurate curvilinear model was, on average, fitting the data in hand only marginally better than the simpler log/log model (albeit much worse than the linear model). The curvilinear model allowed us to construct, in each subject, not only the central value of the QRS duration at heart rate of 60 bpm but also project the individual-specific data to any heart rate. For the purposes of demonstrating the heart rate dependency, we used the projection to the heart rate of 120 bpm.

Race classifications of the subjects were obtained by a race and ethnicity questionnaire. Body weight and body height were measured before the first Holter recording. To account for the differences in body habitus and composition, lean body mass [23] (LBM) was calculated as LBM = 0.29569*W+41.813*H-43.2933 for females and LBM = 0.3281*W+33.929*H-29.5336 for males, where W is body weight in kilograms and H is body height in meters; body mass index (BMI) was calculated as $BMI=W/H^2$.

Observations of physiologic sex and race differences

The ECG data that we present here [14] were obtained from 523 healthy subjects, of whom 254 (48.6%) were females. A total of 236 (45.1%) and 259 (49.5%) subjects classified themselves as of Black/African origin or White/Caucasians, respectively. The others provided other race classifications. The demographic details are shown in Table 7.1. The sex differences in body habitus were as expected but importantly, there were no statistically significant differences (two-sample two-tail t-test) in the age distribution of the subpopulations.

As previously observed in different data [24], we found that in some subjects, the QRS became shorter, while in others, it became longer with increasing heart rate. This observation was made both in females (examples in Fig. 7.1) and in males (examples in Fig. 7.2).

Fig. 7.3 shows the cumulative distributions of the QRS durations measured at heart rate of 60 bpm in different subpopulations of the study. As previously reported, the females had shorter QRS duration (98.74 ± 5.53 ms) than men (103.23 ± 6.01 ms). In addition, African subjects (99.65 ± 5.37) had shorter QRS duration compared to Caucasian subjects (102.31 ± 6.62 ms). When considering the individual sex- and race-defined subgroups, QRS duration progressively increased from African females to Caucasian females to African men to Caucasian men. The cumulative distributions of the QRS duration in the subpopulations also showed substantial overlaps between subpopulations.

The same results were obtained when considering the QRS duration at the heart rate of 120 bpm seconds (Fig. 7.4). The mean values of QRS duration across the subpopulation have not changed much since the numbers of subjects in whom QRS prolonged and shortened at increased heart rate was fairly similar. This is demonstrated in Fig. 7.5 which shows that in both females and men, heart rate increases led to the increases in QRS duration in approximately 40% of the population, while in the remaining 60% of the population, heart rate increases led to QRS complex shortening. Fig. 7.5 also shows that in both

TABLE 7.1 Demographic characteristics of the population from which the presented results were derived.

	African females	Caucasian females	Other females	African males	Caucasian males	Other males
N	111	130	13	125	129	15
ECG number	815 ± 138	787 ± 148	818 ± 151	795 ± 157	812 ± 130	873 ± 110
Age [years]	31.88 ± 8.87	34.62 ± 8.88	33.53 ± 11.2	34.25 ± 7.74	33.38 ± 7.80	32.14 ± 7.92
Body weight [kg]	70.84 ± 9.66	65.38 ± 9.02	65.38 ± 8.44	82.98 ± 11.22	79.17 ± 9.23	75.05 ± 10.15
Body height [m]	1.654 ± 0.063	1.630 ± 0.064	1.587 ± 0.061	1.782 ± 0.073	1.770 ± 0.073	1.762 ± 0.080
LBM [kg]	46.81 ± 4.89	44.19 ± 4.66	42.41 ± 4.55	58.16 ± 5.64	56.49 ± 4.81	54.86 ± 5.3
BMI [kg/m^2]	25.86 ± 2.85	24.59 ± 2.92	25.91 ± 2.56	26.07 ± 2.64	25.27 ± 2.57	24.17 ± 2.81

ECG number shows the number of ECG measurements per subject. *LBM*, lean body mass; *BMI*, body mass index; *ECG*, electrocardiogram

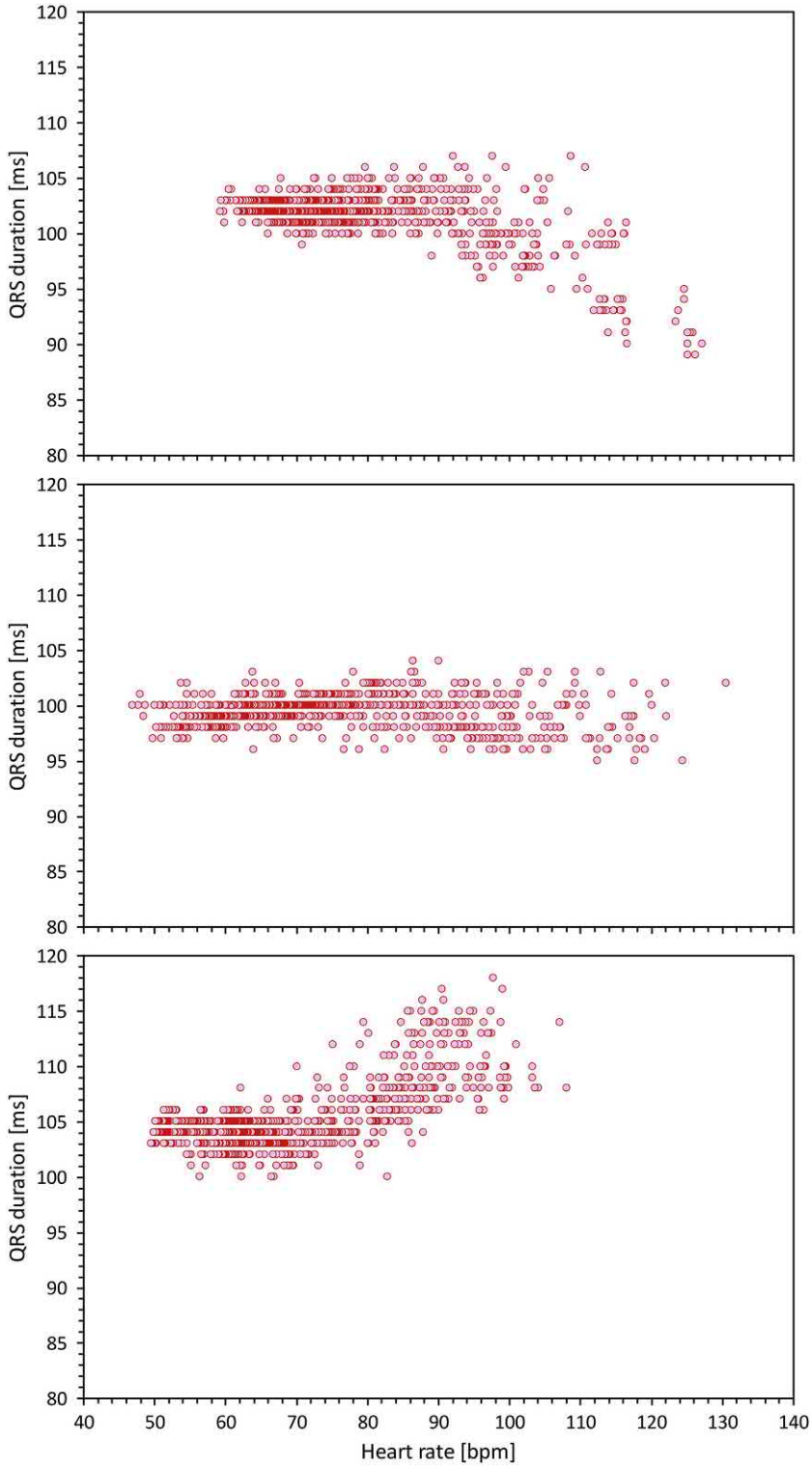

FIGURE 7.1 Examples of QRS/heart rate dependency patterns in three different female subjects. The graphs in the top, middle, and bottom panels show these patterns in females aged 18, 25, and 46 years, respectively.

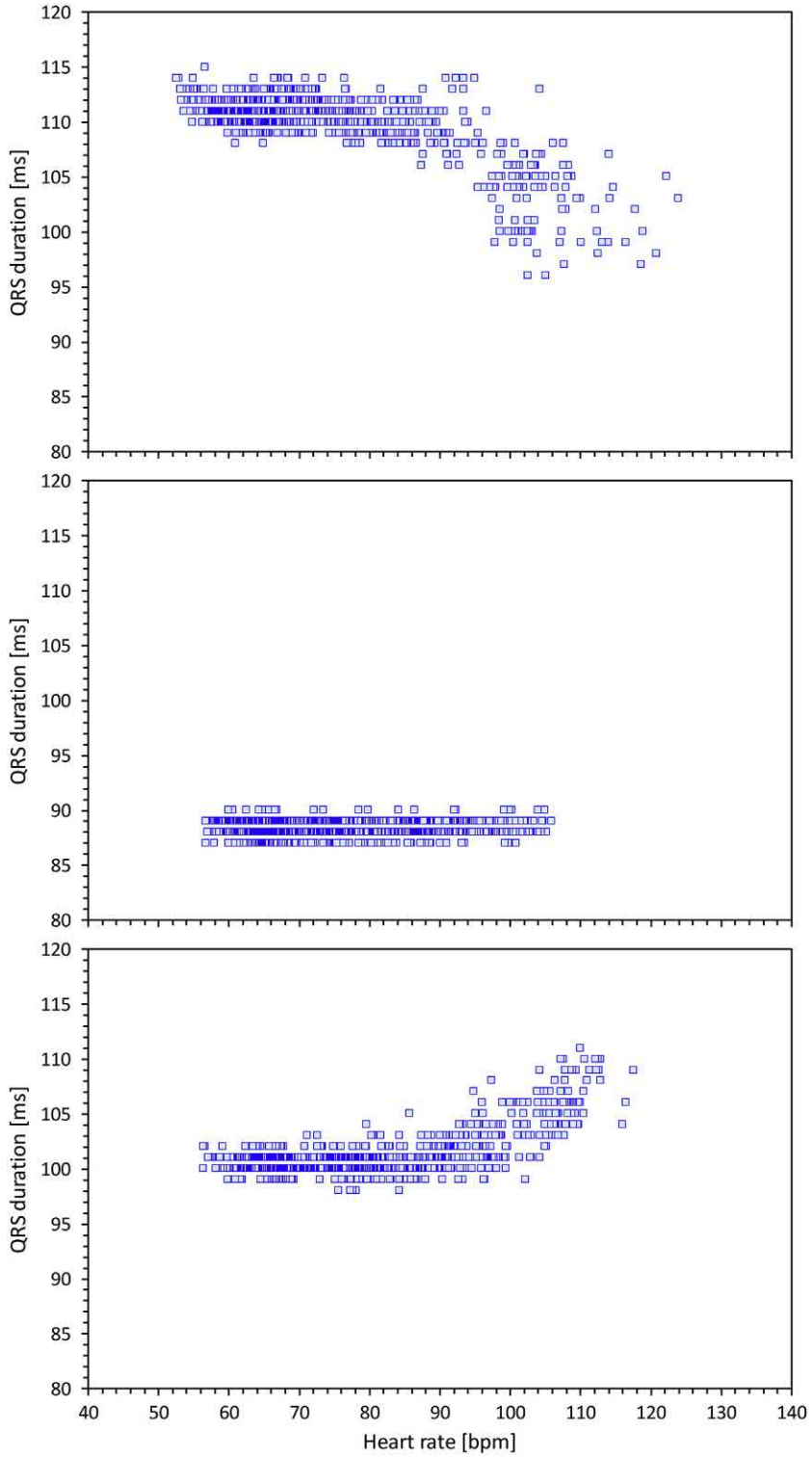

FIGURE 7.2 Examples of QRS/heart rate dependency patterns in three different male subjects. The graphs in the top, middle, and bottom panels show these patterns in males aged 32, 37, and 32 years, respectively.

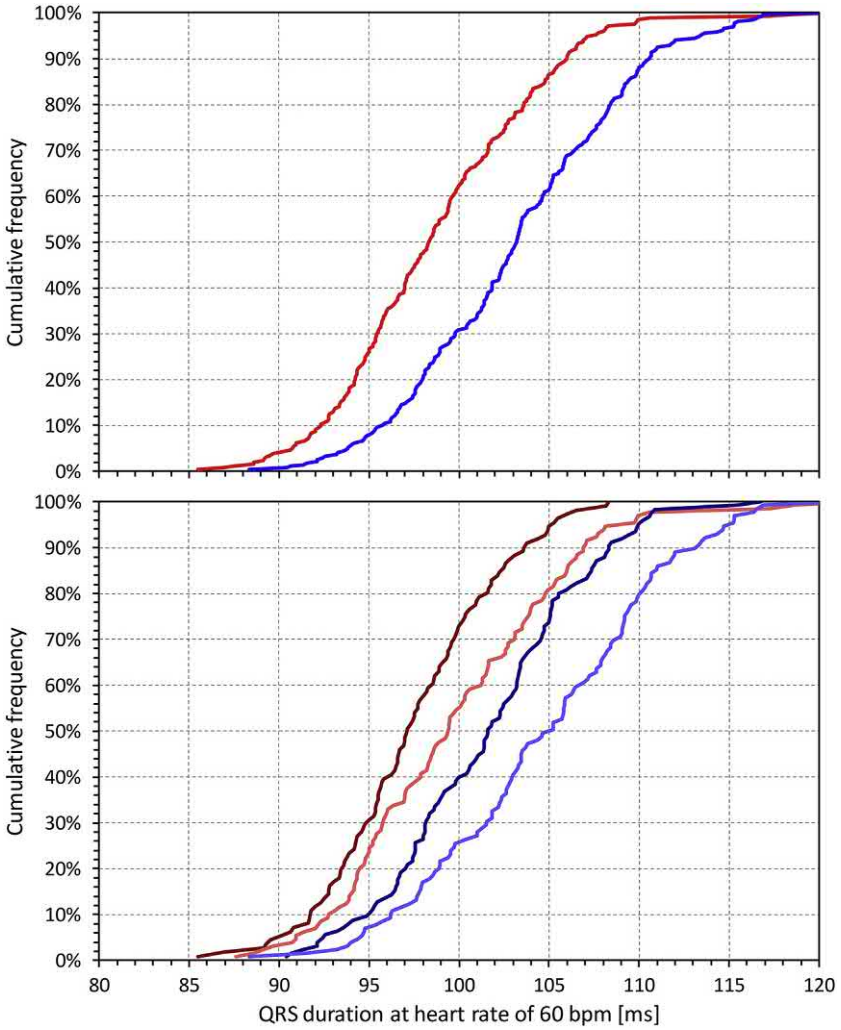

FIGURE 7.3 Cumulative distributions of QRS durations corresponding to heart rate of 60 beats per minute (bpm). The top graph shows the comparison of the distributions in female (*red line*) and male (*blue line)* subjects. The bottom graph shows the comparison between female subjects of African origin (*dark red line*), female Caucasian subjects (*light red line*), male subjects of African origin (*dark blue line*), and male Caucasian subjects (*light blue line*).

females and males, the heart rate−induced QRS changes were unrelated to the QRS duration. (The figure shows this for the QRS duration at heart rate of 60 bpm but the same absence of relationship was observed with QRS durations at different heart rate levels.)

When studying the details of the individual QRS/heart rate patterns, we noted, in agreement with the examples in Figs. 7.1 and 7.2, that in practically all subjects, the QRS width was not changing during slower resting heart rates and only became prolonged or shortened at heart rate faster than some 75−85 bpm. This corresponded to the distributions of the curvilinear QT/RR curvatures shown in Fig. 7.6. Curvature values above 1 signify that the QRS/heart rate pattern is bent upward at the higher heart rate values, while the curvature values below 1 signify pattern that is bent downward. Fig. 7.6 shows minimal sex differences in these curvature value and also shows that the sex difference was more pronounced in subjects of African origin compared to Caucasians. The bottom panel of Fig. 7.6 confirms that there was no consistent relationship between the QRS/heart rate curvature and the age of the investigated subjects.

The observation that the QRS complex duration is more or less stable at slower heart rates and the rate influence appears more manifested only at faster heart rates. It has important implications for the studies of the QRS/heart rate or QRS/RR relationship. In particular, the curved patterns of the relationship make linear regressions between QRS

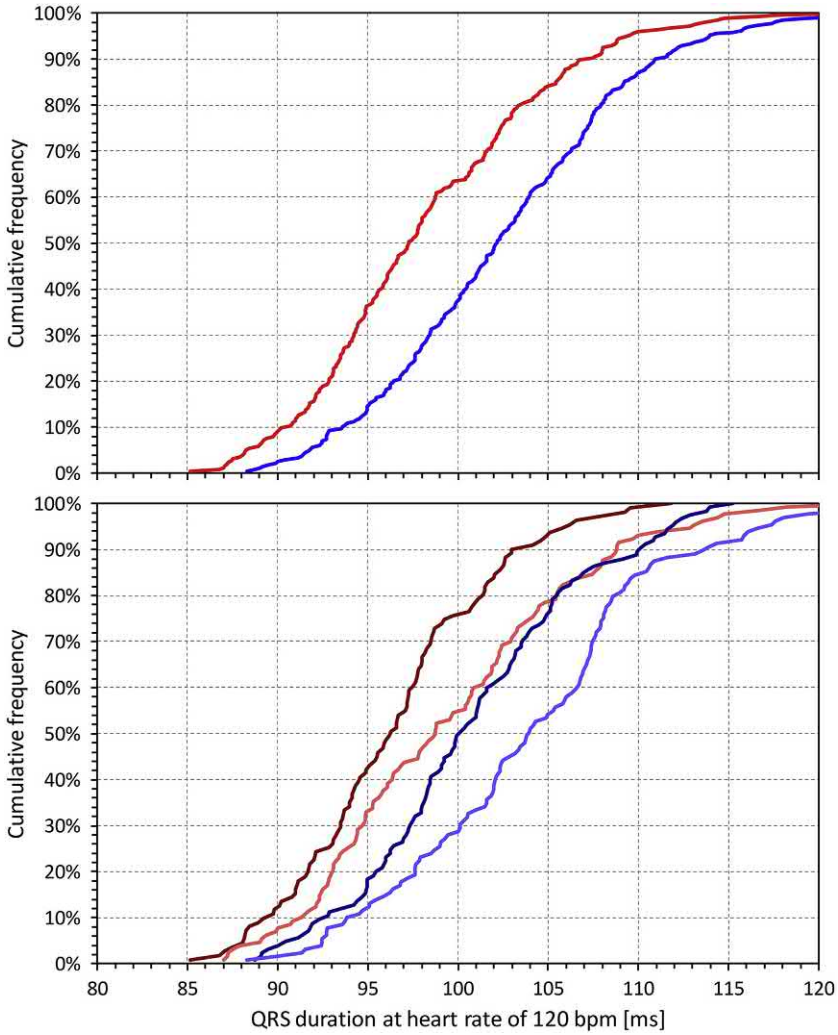

FIGURE 7.4 Cumulative distributions of QRS durations corresponding to heart rate of 120 beats per minute (bpm). The layout of the figure panels and the meaning of the colored lines is the same as in Fig. 7.3.

width and RR interval regression highly inaccurate. In our data, this was documented by the studies of regression residuals which represent the discrepancies between the regression-projected and actual values (that is, the lower the regression residual, the better the regression fit of the data). The comparison of the residuals of the three types of regression models that we investigated is shown in Fig. 7.7. The top two panels of the figure show the cumulative distributions of the residuals of the curvilinear and log/log intrasubject regression models. These panels show that the residuals were moderately lower in females compared to males. Also, while the curvilinear models resulted in better fits of the data compared to the log/log models, the differences were only minimal. On the contrary, the bottom panel of Fig. 7.7 shows the cumulative distribution of the residuals of the linear models and presents several times larger values (note the differences in the spans of the horizontal axes of the panels of Fig. 7.7) and thus substantially poorer fits with the measured data.

Figs. 7.8 and 7.9 show relationships of the QRS duration (measured at the heart rate of 60 bpm) with body weight, body height, BMI, and LBM. The relationship to LBM was the strongest of all these comparisons but still showed only very shallow dependency. This was important to document (in the absence of direct, e.g., echocardiographic heart size measurements) that the sex differences in the QRS duration were not explainable by smaller heart sizes in females.

Finally, Fig. 7.10 shows that in the analyzed population, there was no systematic influence of age on the QRS

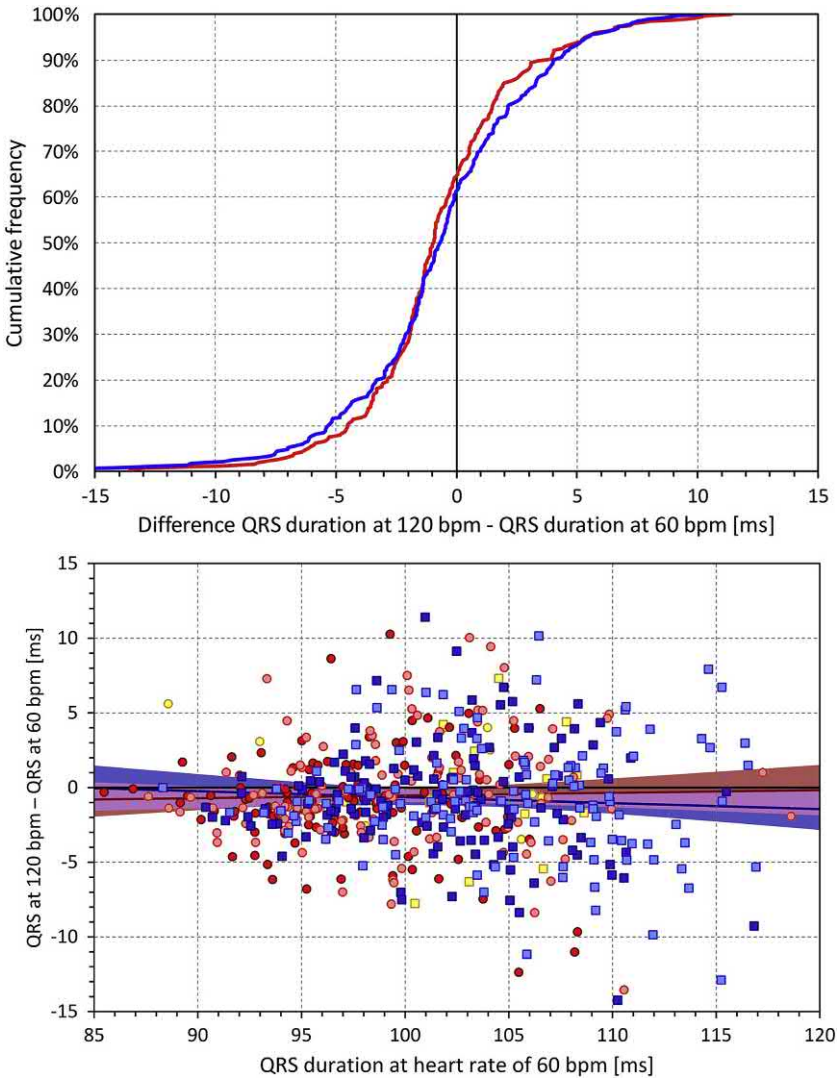

FIGURE 7.5 The top panel shows cumulative distributions of the differences in the QRS durations corresponding to heart rate of 120 and 60 beats per minute (bpm). The distributions in female and male subjects are shown with *red* and *blue lines*, respectively. The bottom panel shows the scatter diagram of the relationship between the QRS duration at 60 bpm and the differences in the QRS durations corresponding to rates of 120 and 60 bpm. African females, Caucasian females, other race females, African males, Caucasian males, and other race males are shown in *dark red circles*, *light red circles*, *yellow circles*, *dark blue squares*, *light blue squares*, and *yellow squares*, respectively. The *red and blue solid lines* show the linear regressions in female and male subjects, respectively; the *light red* and *light blue* areas show the 90% confidence bands of the linear regressions; the *light violet areas* show the overlap between the confidence bands of the sex-specific linear regressions.

duration or on the intrasubject differences of the QRS durations measured at heart rate of 120 and 60 bpm. In other words, the shortening or prolongation of the QRS complex at faster heart rates was unrelated to the age of the subjects.

Interpretation and implications

Our analyses not only confirmed the sex differences but also showed that similar differences in QRS duration that exist between females and males also exist between subjects of African and Caucasian origin. Moreover, the dependency on heart rate is clearly not uniform. At high heart rates, QRS duration is increasing in some subjects and decreasing in others.

This analysis of ECG data in healthy subjects also leads to several observations with potential clinical implications. Considering the potential, albeit speculative implications to the implementation of the guidelines for resynchronization therapy are naturally speculative, the following points might be made.

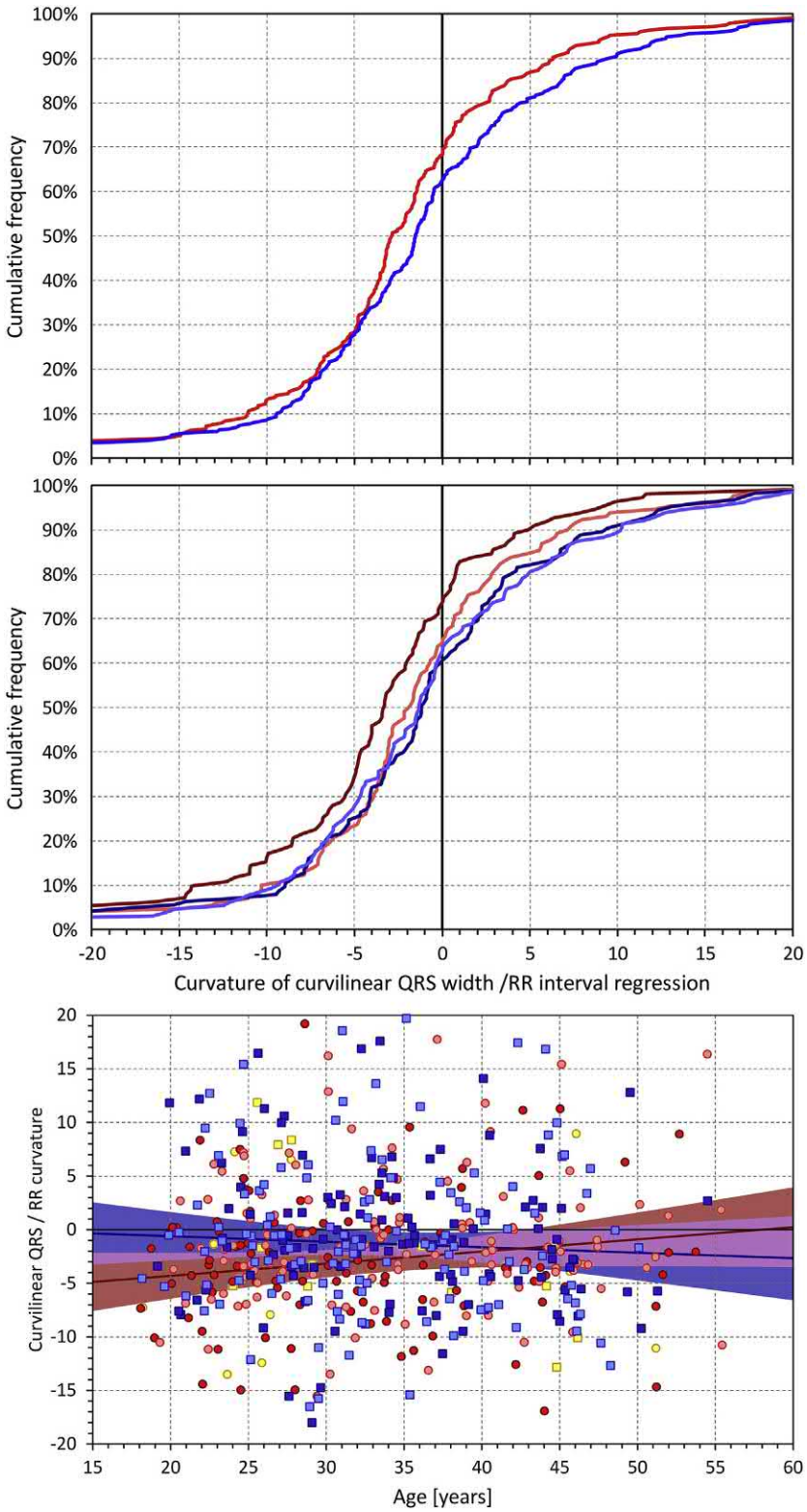

FIGURE 7.6 The top panel shows the cumulative distributions of the curvatures of the curvilinear QRS/RR regressions. The distributions in female and male subjects are shown with *red* and *blue lines*, respectively. The middle panel shows the same cumulative distributions in African females, Caucasian females, African males, and Caucasian males which are plotted with *dark red*, *light red*, *dark blue*, and *light blue lines*, respectively. The bottom panel shows the scatter diagram of the relationship between the ages of the subjects and the curvatures of the curvilinear QRS/RR regressions. The meaning of the symbols, *colored lines*, and *colored areas* is the same as in the bottom panel of Fig. 7.5.

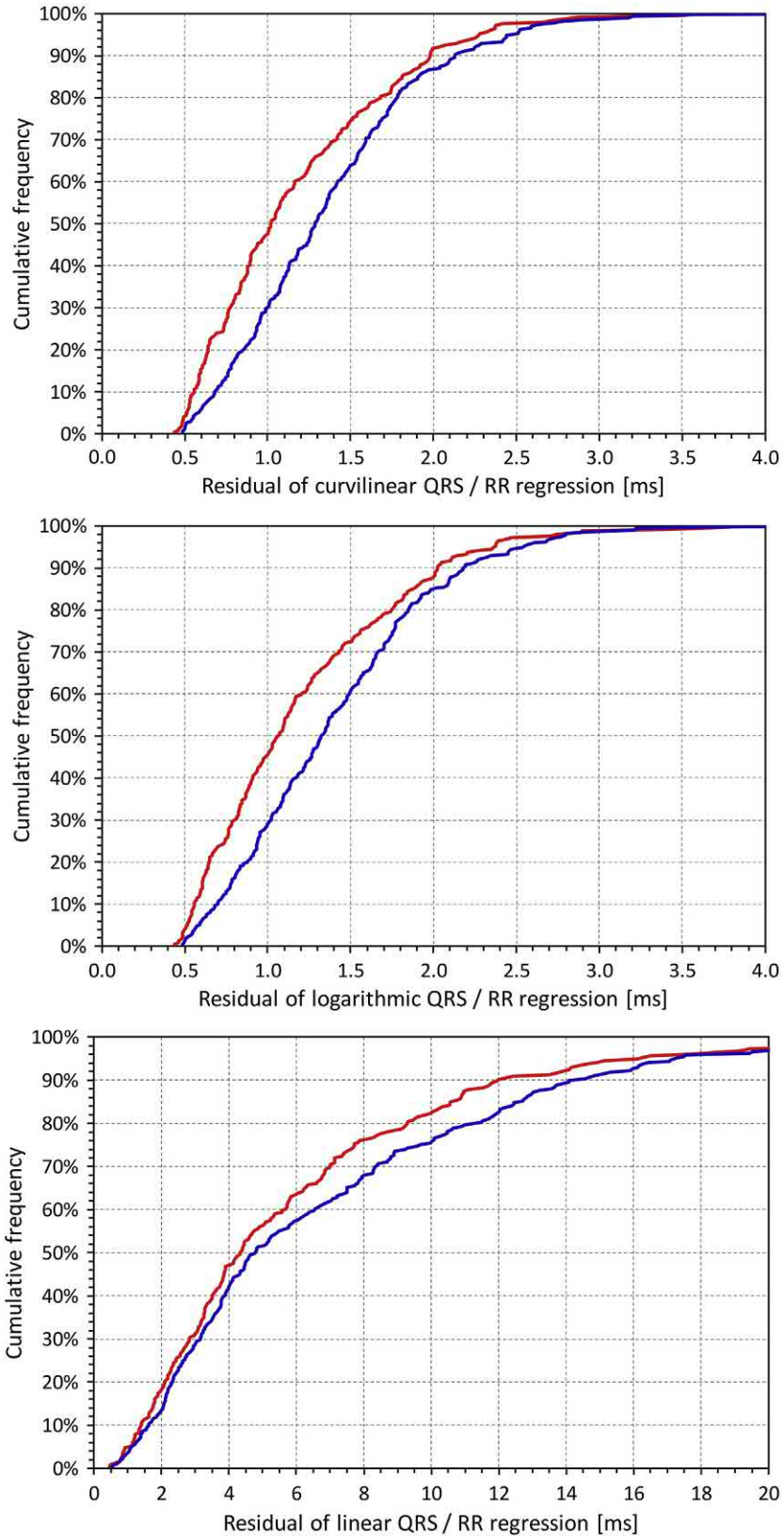

FIGURE 7.7 Cumulative distributions of the regression residuals of the curvilinear, log/log, and linear QRS/RR regression models are shown in the top, middle, and bottom panels, respectively. In each panel, the distributions in female and male subjects are shown with *red* and *blue lines*, respectively.

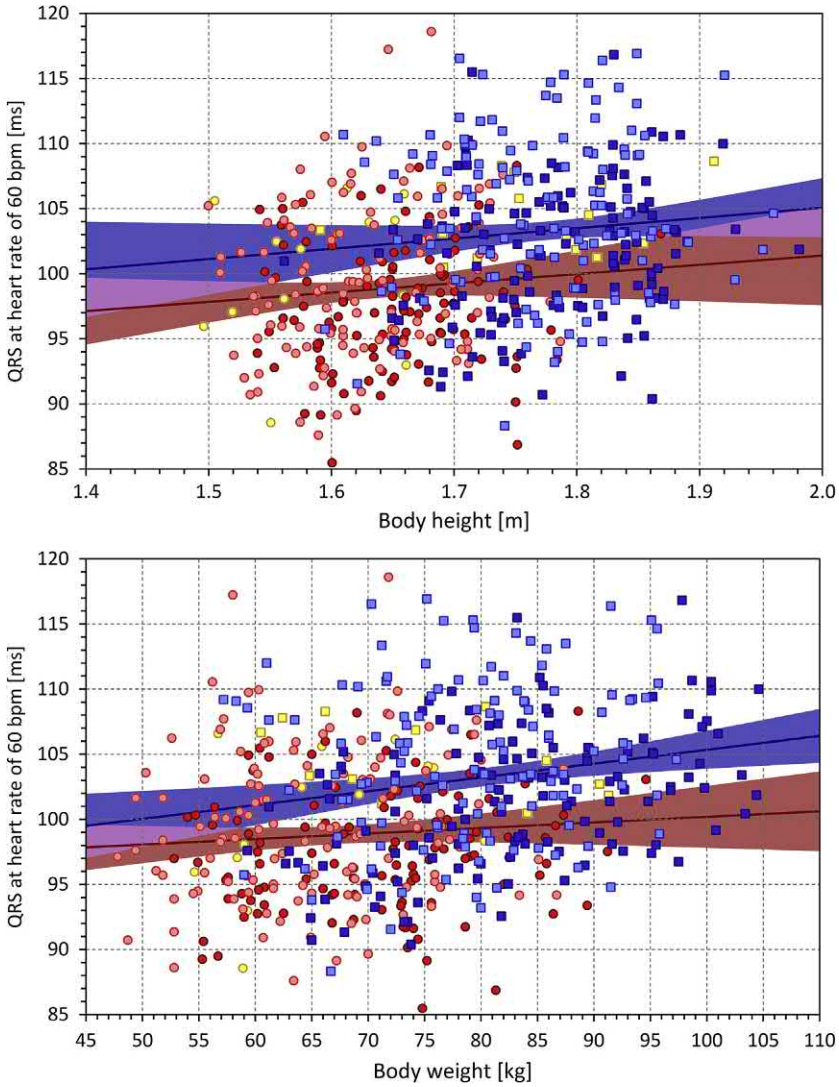

FIGURE 7.8 Scatter diagrams of the relationship between the body height (top panel) and body weight (bottom panel) and the QRS duration corresponding to heart rate of 60 beats per minute (bpm). In both panels, the meaning of the symbols, *colored lines*, and *colored areas* is the same as in the bottom panel of Fig. 7.5.

Firstly, the normal ranges of QRS width appear rather wide. It is very plausible to propose that in patients with conduction abnormalities, QRS width will be similarly widely distributed. Therefore, this should be considered when applying the CRT guideline limits, especially when dealing with QRS measurements close to the limits. QRS prolongation to, say, 125 ms has clearly different clinical meanings not only in African females and in Caucasian males but also in patients with different physiologic pre-pathology conditions.

Secondly, although the images shown in Figs. 7.1 and 7.2 were taken from healthy subjects, it is unlikely that the QRS measurements would be less rate dependent and more stable in cardiac patients. Therefore, multiple measurements should be made to ascertain true QRS duration, especially if dealing with values close to the guideline limits.

Thirdly, similar to healthy subjects, elevated heart rates probably influence QRS durations also in cardiac patients. It might also be speculated that resynchronization therapy would benefit more patients with QRS prolonged at faster heart rates when the hemodynamic demands on ventricular performance are increased compared to the situations at rest. Assessing QRS duration at faster heart rates might therefore be more relevant compared to strictly resting conditions. Some of the

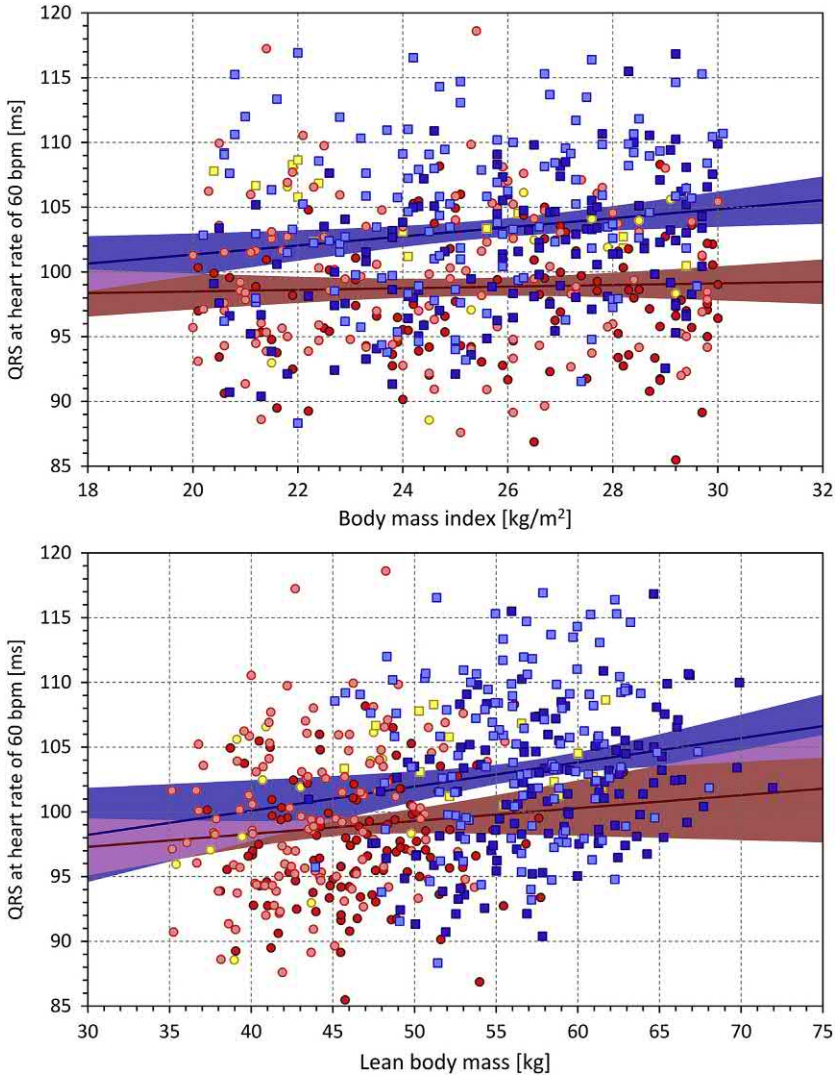

FIGURE 7.9 Scatter diagrams of the relationship between the body mass index (top panel) and lean body weight (bottom panel) and the QRS duration corresponding to heart rate of 60 beats per minute (bpm). In both panels, the meaning of the symbols, *colored lines*, and *colored areas* is the same as in the bottom panel of Fig. 7.5.

previous discussions of the QRS limits used to select resynchronization therapy patients [25,26] might have been contributed by the differences in heart rates at which the QRS measurements were made.

Finally, assuming that the hypothesis is correct that the larger benefits of resynchronization therapy in females are related to their initially shorter QRS durations combined with constant guideline limits [1,27] the same consideration might apply to patients of African origin and Caucasians. On average, patients of African origin might suffer from a more pronounced intraventricular conduction abnormality compared to Caucasian patients showing QRS prolongation above the same limit. Hence, different cardiac resynchronization criteria for patients of African and Caucasian origin might be beneficial.

It is also not obvious why some subjects show QRS shortening and other QRS lengthening at increased heart rates and whether these differences contain predictive information. Based on the data in hand, we can only speculate on the possibilities of QRS lengthening due to subclinical conduction "microblocks" at faster heart rates and of QRS shortening due to sympathetic charges. Only future studies will be able to answer the obvious questions of whether this difference in QRS width response to elevated heart rates makes one of these groups more prone to intracardiac conduction disturbance in the presence of heart failure and consequently to a more positive response to cardiac resynchronization therapy.

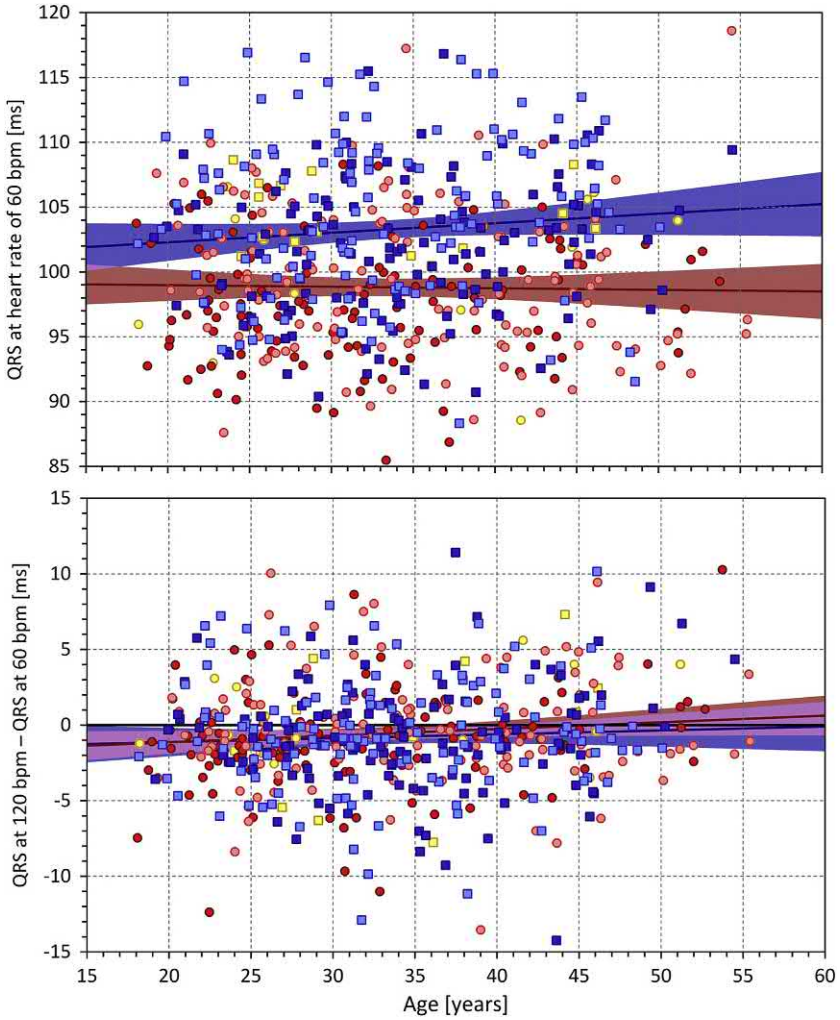

FIGURE 7.10 Scatter diagrams of the relationship between the age of the subjects and the QRS duration corresponding to heart rate of 60 beats per minute (bpm, top panel) and the difference between the QRS duration corresponding to heart rate of 120 and 60 bpm (bottom panel). In both panels, the meaning of the symbols, *colored lines*, and *colored areas* is the same as in the bottom panel of Fig. 7.5.

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Chapter 8

Sex differences in QRS fragmentation and early repolarization pattern

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Introduction

Presence of fragmented QRS complexes (fQRS) or inferolateral early repolarization pattern manifested as end-QRS notching and slurring in standard 12-lead electrocardiogram (ECG) has been associated with adverse cardiac events in previous studies [1,2]. Both of these phenomena take place within the QRS complex. However, fQRS is considered to be a pure depolarization abnormality representing heterogeneous activation of the ventricles due to myocardial scar or ischemia, whereas inferolateral early repolarization is argued to represent repolarization abnormality caused by transient ventricular transmural voltage gradients due to differences in ionic membrane currents. Both, fQRS and some forms of early repolarization pattern, are fairly common findings among healthy subjects [3–5]. Yet, both patterns are associated with adverse outcome in subjects with cardiac disease and some forms of early repolarization even in the general adult population [3,6]. The sex-related differences among these two ECG markers, in terms of their prevalence and prognostic value, have been studied to some extent in the literature. However, the current information is somewhat sparse and conflicting results have been reported. In this chapter we will briefly go through the definition and measurement of these two ECG markers and then explore their sex differences in terms of their prevalence and prognostic value as they are known in the current literature.

Fragmented QRS

Fragmentation of the QRS complex was first observed by Boineau and Cox in 1973, as they experimented with acute ischemia models in canine [7]. The mechanism behind the QRS fragmentation is suggested to stem from heterogeneous activation of the myocardium because of scarring and necrosis of the myocardial tissue secondary to coronary artery disease (CAD). It is believed that scar tissue and areas of myocardial ischemia within viable myocardial tissue form a substrate that promotes disorganized ventricular depolarization by abnormal spatial and temporal impulse conduction which can be seen as notching and slurring of the QRS complex in the surface ECG. In 2006, Das et al. showed that the presence of fQRS correlates with a regional myocardial scar observed in single photon emission tomography among patients referred to nuclear stress test [8]. The sensitivity of fQRS for scar detection in that population exceeded that of the Q wave (86% vs. 36%). Consequently, fQRS in standard 12-lead ECG has been suggested to be an indicator of myocardial scar in patients with CAD, although conflicting results have been reported on its accuracy [9,10]. Previous studies have also shown that fQRS is not specific for CAD as it is commonly seen in nonischemic cardiac diseases as well [11,12]. This suggests that fibrosis, inflammation, and other forms of myocardial damage could induce conduction slowing or blocks which are ultimately manifested as fQRS in the surface ECG. Since the seminal paper from Das et al. [8], several groups have studied the prognostic value of fQRS and found it to be associated with various cardiac disorders and adverse outcome in several patient populations [1]. Interestingly, fQRS is not an uncommon finding in apparently healthy subjects [3,13], which underlines the need for separating the possibly malignant forms of fQRS from the benign forms [14].

Definition of fragmented QRS

Das et al. defined fQRS in subjects with normal QRS duration (<120 ms) as an additional R wave (R′ or r′) or notching of the R or S wave in at least two contiguous leads corresponding to a major coronary artery territory (Fig. 8.1)

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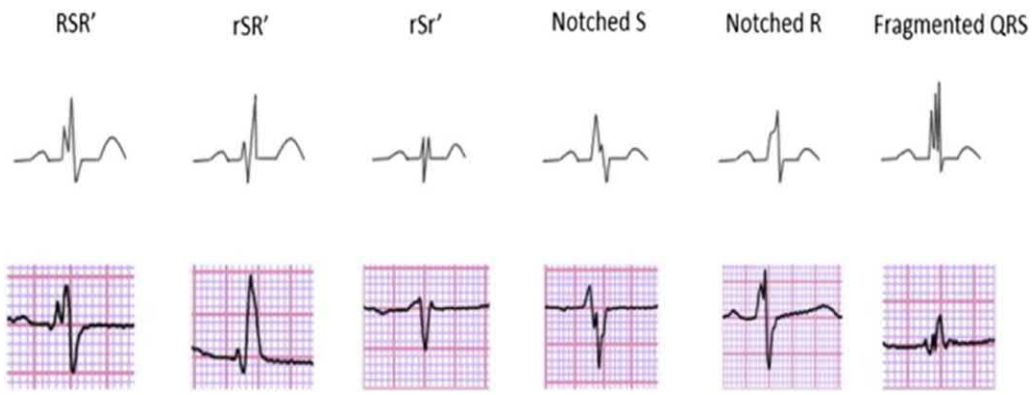

FIGURE 8.1 Illustration of various fragmented QRS morphologies as seen on 12-lead electrocardiogram [3]. *Reprinted with permission from Elsevier.*

[8]. These regions were defined as inferior (leads II, III, aVF), anterior (leads V1 to V5), and lateral (leads I, aVL, V6), although other lead combinations have been used in defining different regions in other studies [3,15]. According to the criteria, the fQRS pattern can have multiple spikes or a slurred form, which can be observed as a shoulder on the side of the R wave. The criteria do not define amplitude thresholds for the notches, but others have applied these in their work. For instance, Vogels et al. set criteria for the maximum amplitude ratio (6:1) between the notch and the wave in which the notch was inscribed in Ref. [15]. This could be beneficial in separating between noise and actual fragmentation. Vogels and colleagues also required that fQRS was present in >50% of the QRS complexes within a single lead [15].

Initially the fQRS criteria excluded subjects with wide QRS complexes (≥120 ms), but later separate criteria were developed for these cases [16]. In subjects with prolonged QRS duration due to, e.g., paced rhythm, premature ventricular complexes (PVC), or bundle branch block (BBB), fragmented wide QRS complex (f-wQRS) is considered to be present if >2 notches, i.e., two additional notches, are observed in the R or S wave in at least two contiguous inferior, lateral, or anterior leads (Fig. 8.2). According to the criteria, PVC can be considered fragmented with only two notches if these are located in the R wave >40 ms apart from each other and observed in at least two contiguous leads. The sensitivity and specificity of f-wQRS for detecting myocardial scar were 87% and 93% [16], which were similarly reported for the fQRS in narrow QRS complexes (86% and 89%, respectively) [8].

Although the fQRS criteria by Das might be the most widely used, it is not the only one. Some have suggested that fQRS should be graded more thoroughly instead of using binary grading for it [14,17]. The criteria by Das do not take into account the number of leads affected, the amplitudes of the notches, or the fQRS morphology, all of which might play a significant role in the prognostic value of this marker. Therefore, future studies are needed to shed some light on the clinical value of these features. However, the most significant disadvantage of fQRS is its visual grading. Fragmentation suffers from the same flaw as rest of the electrocardiographic measures that are dependent on subjective interpretation; it is not very reproducible as it is highly dependent on the person who is grading it [18,19]. Fortunately, there are ongoing efforts toward automated detection of fQRS from digital ECG, which could aid the assessment of true clinical value of this marker, as with computerized measurements results are more reproducible and accurate than manual measurements [17,20].

When grading ECG for fQRS, whatever the set of criteria used, be it for manual or digital measurements, it is good to review the filter settings for the ECG machine first, as these settings have direct impact on the detection of fQRS notches. If the low-pass filter is set too low (e.g., 40 Hz or below), the notching pattern could be filtered out or at least the amplitude will be reduced drastically. ECGs recorded in the 0.05−100/150 Hz frequency range have been suggested to yield better sensitivity in identifying fQRS. It is also good to acknowledge that if magnification is used, either in paper or digital measurements, the prevalence of fQRS is likely to increase, as smaller and smaller notches are made visible via the magnification.

Prevalence of fragmented QRS and sex differences

In previous studies, the prevalence of QRS fragmentation has been associated with older age, male sex, and the overall cardiac health of subjects [3]. Therefore, it depends entirely on the population it is examined in (Fig. 8.3). The prevalence of fQRS in healthy adults has been reported to be 5%, with 7% prevalence among men and 3% prevalence among women [13]. Majority of the fragmentation observed in this study was in inferior leads (86.8%), which

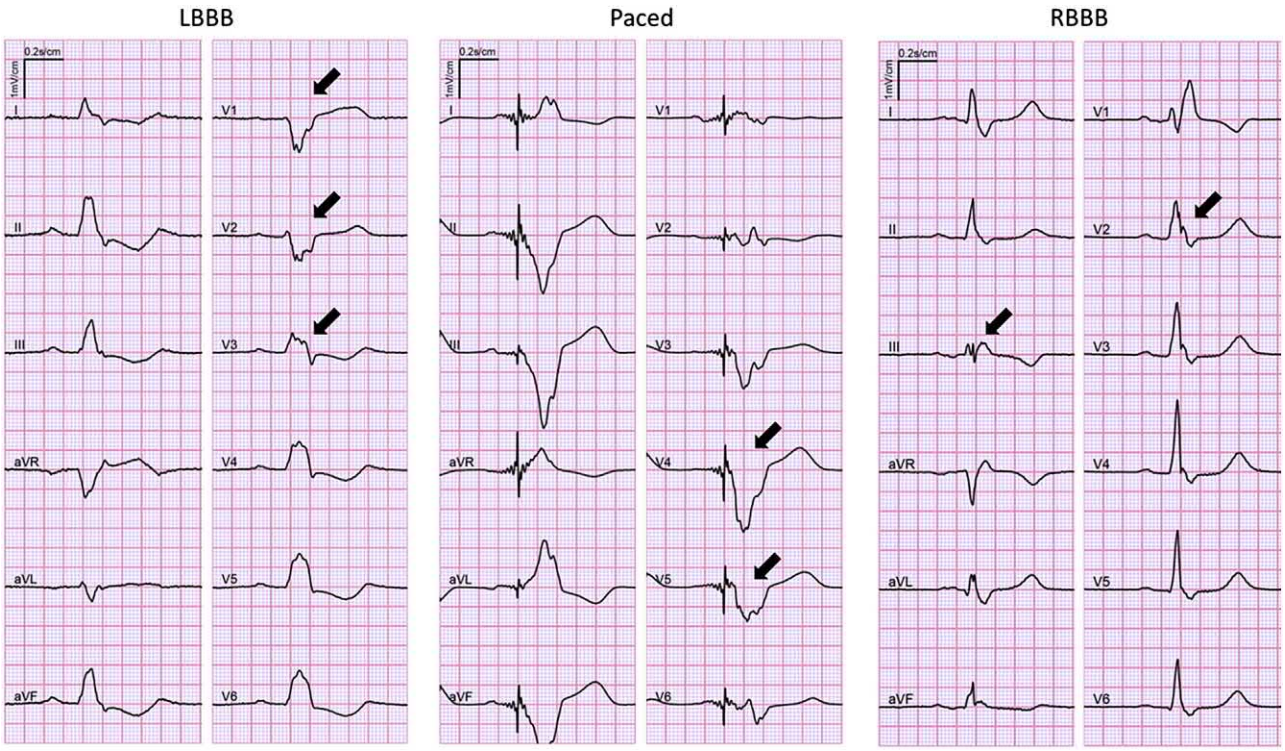

FIGURE 8.2 Fragmented wide QRS complexes due to left bundle branch block (LBBB) (left), paced rhythm (middle), and right bundle branch block (RBBB). Fragmented complexes are indicated with *black arrows*.

was suggested to stem from more leftward frontal QRS axis among the participants [13]. In the Finnish Mobile Clinic Health Survey population, drawn from the general adult population between 1966 and 1972, fragmented QRS was observed in up to 18% of subjects with no clinical or electrocardiographic evidence of cardiac disease [3]. In this study as well, majority of fragmentation was observed in the inferior leads (86.6%), whereas fragmentation in anterior and lateral leads was less frequent (16.1% and 2.8% of the fQRS cases, respectively) [3]. In this group of subjects with no apparent cardiac disease, men had more often fQRS than women (20.5% vs. 14.8%, $P < .001$). This difference was largely explained by more frequent fragmentation of the inferior leads among men (19.0% vs. 12.6%).

In subjects with known or suspected CAD, QRS fragmentation can be observed in approximately 20%–35% of cases [8,21]. In the Mobile Clinic study [3], the prevalence of fQRS in subjects with suspected or known cardiac disease was 22.3%, with significantly higher prevalence among men (25.4% vs. 15.8%, $P < .001$). In the

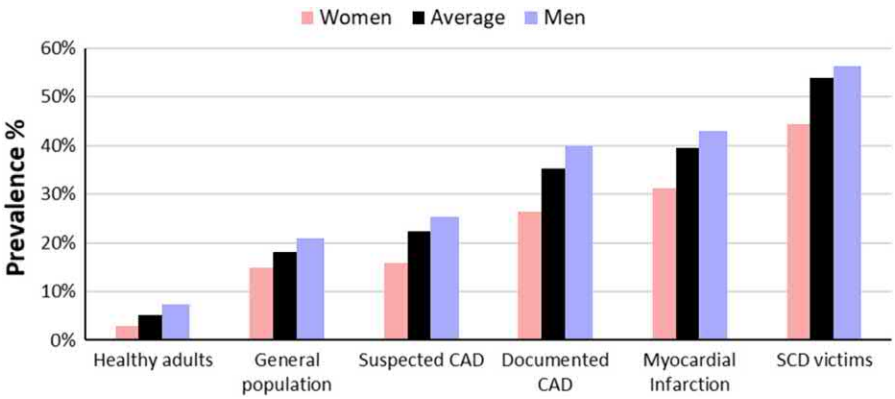

FIGURE 8.3 Prevalence of QRS fragmentation in different populations. Fragmentation is clearly related to the underlying cardiac health in both men and women. However, women seem to have significantly lower prevalence of fQRS in each population compared with men. *CAD*, coronary artery disease; *SCD*, sudden cardiac death.

ARTEMIS study [22], QRS fragmentation was observed in 35.3% of patients who had angiographically documented CAD with ≥50% occlusion in one of the main coronary arteries but no prior myocardial infarction. In this subset of patients, 39.9% of men and 26.4% of women had QRS fragmentation. If prior myocardial infarction had occurred, the prevalence of fQRS rose to 39.5%, with 42.9% of men and 31.2% of women exhibiting fQRS. This is in line with other studies reporting on the prevalence of fQRS among patients with myocardial infarction [23]. Among victims of sudden cardiac death (SCD), the prevalence of fQRS is even higher. In the Fingesture study [24], which systematically collected clinical and autopsy data from 5869 SCD victims between 1998 and 2017, the prevalence of fQRS was 53.8% among adult victims of SCD (aged 30−80 years) with premortem ECG. The prevalence of fQRS was significantly higher among men than among women (56.1% vs. 46.0%, $P = .009$). When the histological samples from the autopsy were analyzed, gradual increase in the prevalence of fQRS was observed with increasing degree of myocardial fibrosis (Fig. 8.4).

Prognostic value of fragmented QRS and sex differences

The presence of fQRS is suggested to implicate heterogeneous activation of the myocardium because of myocardial damage, which creates a milieu for reentry and malignant ventricular arrhythmias. In previous studies, fQRS has been associated with adverse outcome in different patient populations [1]. Among patients with ischemic heart disease, fragmented QRS has been associated with more frequent hospitalizations because of heart failure [25], increased risk of mortality [1,8,16,21], cardiac death [25], and ventricular arrhythmias [26,27]. Some studies have identified fQRS as an independent predictor of SCD [3,27]. Among nonischemic patients, fQRS has been associated with ventricular arrhythmias and increased mortality [15,27]. However, sex differences related to the prognostic value of fQRS have not been studied extensively. Part of the reason for this lack of knowledge might be because of the higher risk of cardiac diseases and events among men. Due to this disparity, majority of the previous studies exploring the prognostic value of fQRS have had predominantly male subjects (70%−98% of the subjects). This on the other hand reduces the chances of exploring interaction between sex and fQRS, as statistical power would not be sufficient to distinguish differences between sexes.

In a previous study among healthy adults from China, none of the subjects with fQRS had any adverse outcomes during a 3-year follow-up [13]. Similarly in general population, among subjects with no evidence of cardiac disease, fQRS was not predictive of arrhythmic, cardiac, or all-cause mortality during a long-term follow-up [3]. These findings support the concept that isolated fQRS, in the absence of known or suspected cardiac disease, is not a specific marker of increased risk of mortality. However, in the presence of known or suspected cardiac disease, lateral fQRS was associated with increased risk for arrhythmic (HR: 3.0, 95% CI: 1.4−6.6, $P < .004$), cardiac (HR: 2.5, 95% CI: 1.5−4.2, $P < .001$), and all-cause mortality (HR: 1.9, 95% CI: 1.3−2.7, $P < .001$). In this study population, no statistically significant interaction between sex and prognostic value of fQRS was observed. However, among subjects with QRS fragmentation, men had overall higher mortality rates than women with respect to sudden arrhythmic death (8.1% vs. 4.4%) and cardiac death (18.4% vs. 13.7%) during the 30-year follow-up. In the ARTEMIS study, no statistically significant interaction was observed between sex and the prognostic value of fQRS among subjects with documented CAD, with or without prior myocardial infarction. Among fQRS cases with documented CAD but no previous myocardial infarction, men had higher rates of SCD (2.3% vs. 0%), cardiac death

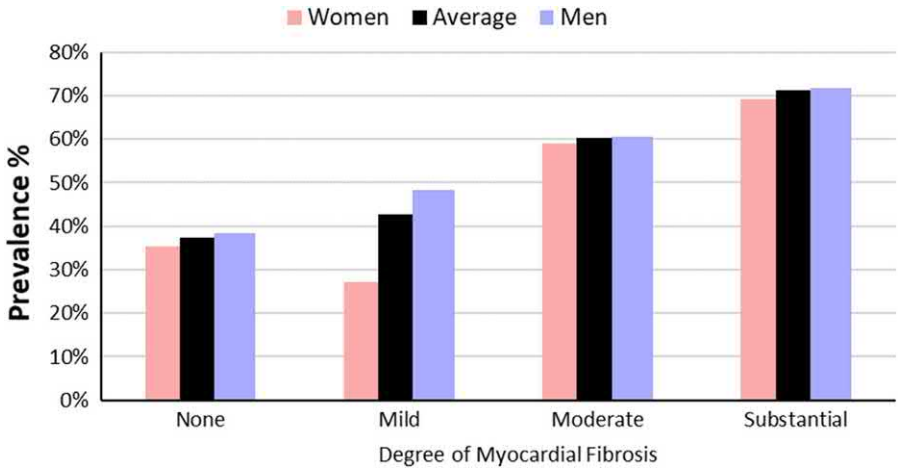

FIGURE 8.4 Prevalence of QRS fragmentation with respect to histological samples from autopsy data among victims of sudden cardiac death.

(4.2% vs. 0%), and overall mortality (11.5% vs. 6.0%) than women. Among fQRS cases with CAD and previous myocardial infarction, women had higher rates of SCD (2.9% vs. 4.8%), cardiac death (6.6% vs. 8.4%) but lower rate of overall mortality (12.4% vs. 10.8%). Although the results from the ARTEMIS study hint that postmyocardial infarction women might be at higher risk than their male peers, it is worth noting that the study lacks statistical power as the number of endpoints was quite low. Therefore, further studies are needed to explore the possible interaction between sex and the prognostic value of fQRS.

Early repolarization pattern

Electrocardiographic pattern of early repolarization in the precordial leads has been considered a benign finding for more than half a century. As this marker is generally observed among young and fit individuals, it has been associated with good health [2,5]. However, early repolarization pattern manifested as terminal notching or slurring of the QRS complex in inferolateral leads was later associated with vulnerability to ventricular fibrillation in independent case–control studies [28,29]. Subsequently, it was noticed that this electrocardiographic pattern was an independent predictor of cardiac and arrhythmic death in the general population [6], especially when present in the inferior leads and accompanied by horizontal or descending ST segment [30]. The mechanism behind the early repolarization pattern is somewhat under debate as to whether the phenomenon is caused by repolarization or depolarization abnormalities [31]. Repolarization mechanism is supported by studies in ventricular wedge preparations indicating that J-wave patterns arise from transmural repolarization gradients due to differences in ionic membrane currents, such as I_{to} [32]. The depolarization mechanisms on the other hand are supported by studies suggesting that structural discontinuities could cause conduction disturbances and give rise to end QRS notching [33]. However, it seems plausible that both forms are possible in human [31]. This debate has also led to dispute over the terminology used to describe this phenomenon. Term early repolarization is often considered confusing, as many associate it with the benign-ST-segment elevation usually observed in precordial leads—a common finding among athletes. J-point elevation or J wave has been suggested, but this terminology is confusing as well as many consider J point as the onset of ST segment while others take it as the peak or onset of end-QRS notch. Some have even suggested an umbrella term for J-wave syndromes, which brings together Brugada syndrome and different forms of inferolateral J-wave patterns. In this chapter we will use the term early repolarization pattern to describe the end-QRS notching and slurring pattern in inferolateral leads with or without ST-segment elevation.

Definition of early repolarization pattern

The term early repolarization has been used for decades and its definition has varied during that time [34]. The classical definition of early repolarization was either ST-segment elevation or a combination of ST-segment elevation and terminal QRS slurring or notching, whereas the new definition adopted by Haïssaguerre and colleagues [28] concentrated on the end-QRS notching and slurring in inferolateral leads, irrespective of the morphology of the ST segment (Fig. 8.5). Recent consensus papers [2,34] have tried to reduce the confusion surrounding the terminology and the measurement of this phenomenon. These papers have defined early repolarization pattern as end-QRS notching or slurring, with or without ST-segment elevation, occurring in at least two contiguous leads of the 12-lead ECG (excluding V1 to V3), with J-point elevation of $\geq$0.1 mV measured from the level of the QRS onset and QRS duration $<$120 ms (Fig. 8.5). Duration of the QRS complex, in the presence of early repolarization pattern, should be measured using only those leads that do not exhibit the pattern. In addition, the end-QRS notching and slurring should occur on the final 50% of the downslope of a dominant R wave so that the QRS complex links with the ST-segment without a negative part in between.

Prevalence of early repolarization pattern and sex differences

Owing to the different definitions used for the early repolarization pattern and differences in measurement techniques, early repolarization pattern has been reported to occur in 2%–31% in the normal population [35]. This variation could also be related to the selection of subjects as the prevalence of early repolarization is highly dependent on demographic factors, such as age and sex of the population as well as race and physical fitness. The prevalence of early repolarization seems to have its peak during the early decades of life and then gradually decreases with older age in both sexes (Fig. 8.6). Almost all previous studies have reported higher prevalence among men [35], with highest rates observed among young men. Not surprisingly, clear linkage and dose-effect has been observed between the early repolarization pattern and testosterone levels among men [36], with significantly higher testosterone levels observed among men with early repolarization pattern than those without. Possible mechanism behind this

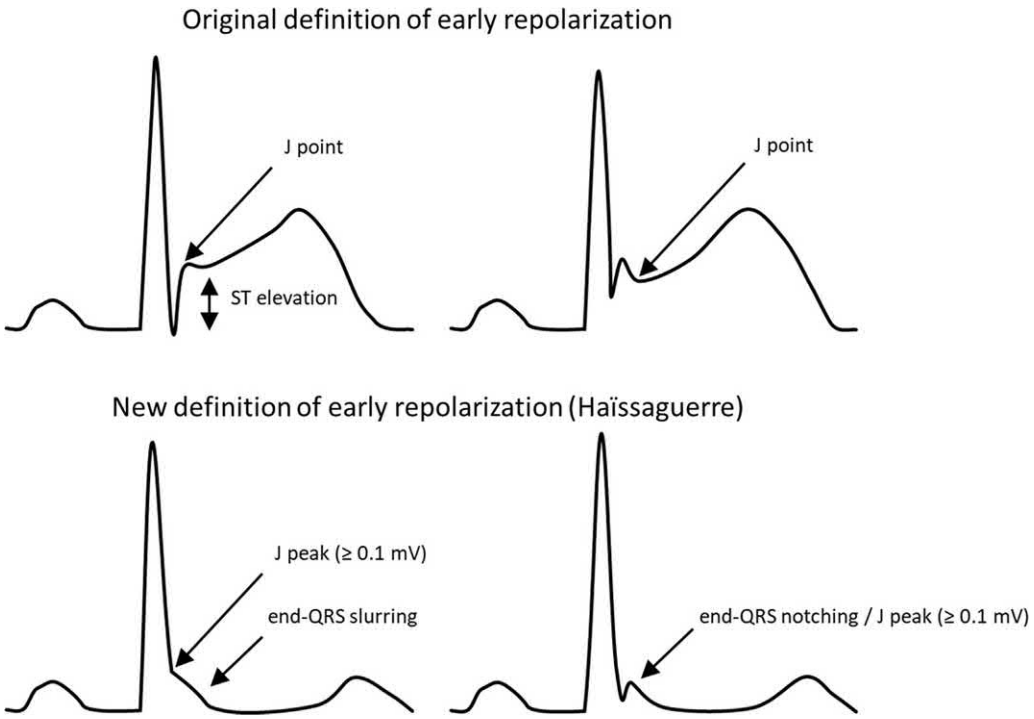

FIGURE 8.5 The figure shows the classical definition of early repolarization with ST-segment elevation with and without QRS notching (top). On the bottom is illustrated the new interpretation of early repolarization pattern, which is defined as end-QRS notching or slurring (≥0.1 mV) in at least two contiguous inferior or lateral leads.

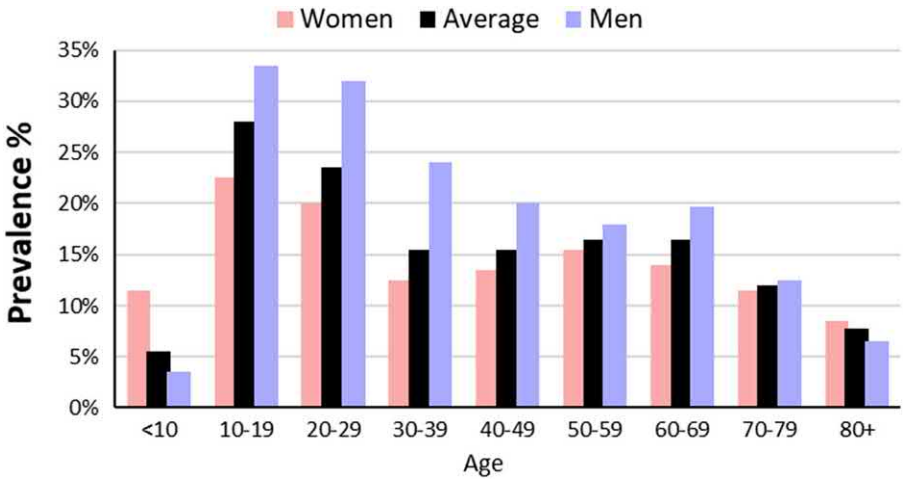

FIGURE 8.6 Prevalence of J-point elevation at different ages among men and women without overt heart disease. *Reprinted from Lanza GA, Mollo R, Cosenza A, Pinnacchio G, Careri G, Laurito M, et al. Prevalence and clinical correlates of early repolarization and J wave in a large cohort of subjects without overt heart disease. J Electrocardiol 2012;45(4):404–10, with permissions from Elsevier.*

testosterone effect might be related to testosterone increased outward repolarizing currents, such as I_{to}. Although the prevalence of early repolarization pattern is significantly higher among men in the early decades of life, the difference between the sexes diminishes after middle age and then declines steadily with older age.

The location of the early repolarization pattern seems to vary between the sexes, as men tend to have more frequently inferior J-wave elevation than women, whereas women seem to have more frequently lateral localization of the pattern [30]. The early repolarization pattern accompanied by ascending ST segment is significantly more frequent

among men (88%), whereas the early repolarization pattern with horizontal/descending ST segment was only slightly dominated by men (57%). Vast majority (93%) of widespread early repolarization pattern (observed in both inferior and lateral leads) was also observed in men.

Prognostic value of early repolarization pattern and sex differences

There are conflicting results on the effect of sex and prognostic value of the early repolarization pattern in the current literature, especially those drawn from the general adult population. This might in part be due to the relatively small prevalence and the male predominance of this electrocardiographic pattern, whereby studies reporting prognostic value of the early repolarization pattern have often too small sample size to reliably investigate interaction between sex and early repolarization pattern. This is even more challenging when dealing with rare endpoints such as SCD, which has an estimated yearly incidence of 1−2/1000 persons per year in the general population. One of the largest studies from the general adult population applying the above-mentioned criteria for the early repolarization pattern was by Tikkanen et al. In this population, men with early repolarization pattern had higher overall incidence of arrhythmic (14% vs. 6%) and cardiac death (28% vs. 15%) than women with early repolarization pattern during the 30-year follow-up. Similarly, Sinner et al. reported two to fourfold risk for all-cause and cardiac mortality among men between 35 and 54 years of age with the early repolarization pattern in the German MONICA database, whereas women with early repolarization pattern were not at higher risk for all-cause or cardiac mortality within any age group [37].

Some studies have suggested that women might in fact be at higher risk. In the study by Rollin et al. [38], the authors reported findings from a population-based study in France, which indicated that women with early repolarization pattern had fourfold greater risk of all-cause mortality over men during a long-term follow-up. After adjustments, the risk for all-cause mortality was 1.9 (95% CI: 1.0−3.7) among men and 4.8 (95% CI: 1.9−12.2) among women. They also reported a significant interaction between sex and early repolarization pattern in noncardiovascular mortality with no significant risk among men (HR: 1.2, 95% CI: 0.5−2.9), whereas women had 4.1-fold risk (95% CI: 1.3−13.2) for noncardiovascular mortality. No significant interaction between sex and early repolarization pattern was observed for cardiovascular mortality, as there was a 4.7-fold risk (1.7−13.1) among men and 7.1-fold risk among women (95% CI: 1.3−32.2). However, their study had limited statistical power as the number of women with early repolarization pattern was only 33, of which 6 died during the follow-up. Two other studies have also suggested higher risk for women, but these studies have used ST-segment elevation in at least one lead to define early repolarization [39,40]. A meta-analysis combining roughly 200,000 subjects from 16 studies hinted that women with early repolarization pattern might be at higher risk for sudden cardiac arrest, cardiac death, and all-cause mortality than men, but the interaction was not statistically significant [41].

Overall, vast majority of studies using the above-mentioned criteria have shown that early repolarization pattern manifested as end-QRS notching and slurring, especially in the inferior leads, is associated with increased risk of all-cause, cardiac, and arrhythmic death [2]. Few studies have reported negative findings, which might be in part explained by the selection of patients—in terms of age, sex, or race—or relatively short follow-up period. However, it seems that some forms of early repolarization pattern are less harmful than others. Lateral early repolarization and slurred early repolarization have been suggested to be more benign features than inferior and notched forms [6,41]. According to several studies, there is evidence that early repolarization pattern with rapidly ascending ST segment in inferior or lateral leads of a 12-lead ECG, which is frequently observed in young healthy athletes with structurally normal hearts, is actually a benign variant, whereas subjects with horizontal or downsloping ST segment are at higher risk for [30,41,42]. This hypothesis has been backed up by several studies and metaanalyses. It is an important piece in the puzzle of determining benign early repolarization from the malignant form. Based on the vast amount of data gathered so far, it seems that inferolateral early repolarization pattern among asymptomatic subjects without previous heart disease or family history of SCD seem to be having only a minimal risk of adverse outcome. Nevertheless, future studies are needed to distinguish specific patient characteristics and early repolarization pattern features that are associated with increased risk of adverse outcome.

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Chapter 9

QT interval duration and *QT*/heart rate relationship

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The *QT* interval, defined as the duration between the onset of the QRS complex and the end of the T wave, is one of the most essential interval measurements characterizing electrocardiogram (ECG) recordings. As well known, the duration of the *QT* interval is heart rate dependent although the details of this dependency and the most appropriate way of correcting the *QT* interval for heart rate are still being debated. It is also well known that when the *QT* interval is corrected for heart rate with a reasonable accuracy, the rate corrected *QTc* intervals are longer in females that in males [1−3].

For a number of clinical reasons, the duration of the *QTc* interval is of clinical importance [4]. This spans from the diagnosis of congenital channelopathies that modify myocardial repolarization processes [5] and estimating cardiovascular risk [6], to ensuring clinical safety of drugs that are known to affect ventricular repolarization [7]. Both abnormally short and abnormally long *QTc* interval durations may signify increased risk of tachyarrhythmias. For this reason, *QTc* interval duration is also intensively studied in clinical pharmacology studies of novel pharmaceutical compounds with the aim of identifying those drugs that might have undesirable proarrhythmic properties [8].

This chapter summarizes electrocardiographic measurements of the *QT* interval, the relationship of the *QT* interval duration to the underlying heart rate, and appropriate methods for accurate heart rate correction of the *QT* interval. It shows that the differences between females and males can be found in these aspects of myocardial repolarization.

Electrocardiographic measurements

The prevailing clinical practice is not particularly accurate in terms of *QT* interval measurement since, frequently, printouts of 12-lead ECGs (25 mm/s paper speed, 10 mm/mV amplitude) are used to measure *QT* interval duration in lead II.

As well known, the interlead discrepancies in the *QT* interval measurement are caused, apart from measurement inaccuracies, mainly by the different projection of the spatial T-wave loop into the different ECG leads [9−11]. The frequent selection of lead II for *QT* measurement is possibly influenced by the simple technical fact that in standard ECG displays, most electrocardiographic machines show the full rhythm strip in lead II. Nevertheless, lead II is habitually considered to contain the longest and thus the most representative *QT* interval duration. Such an assumption is not supported by data. For instance, Fig. 9.1 shows analysis of more than 8000 digital ECGs recorded in healthy subjects in supine positions. In each of these ECGs, the *QT* interval duration was measured by two or more independently working cardiologists, with averaging five different measurements of the given lead and with reconciliation of disagreements between the observers. The *QT* interval duration in lead II was the longest of all leads only in some 11% of the cases and its difference from the true maximum reached 50 ms in some cases. This does not mean that other singular ECG leads would be clearly preferable to lead II. As seen in Fig. 9.1, similar inconsistencies also exist with measurements made in other leads. This is not surprising, since the T-wave lead projection depends on the actual orientation of the spatial T-wave loop. This is not only individual but also dependent on position of the heart in the thorax which, in turn, depends not only on body position but also on meal ingestion and many other factors. Thus, in daily practice, when the *QT* interval duration determines important clinical decisions, single-lead measurements should not be relied on. Assurance of the validity of the measurement comes from the mutual correspondence between different ECG leads.

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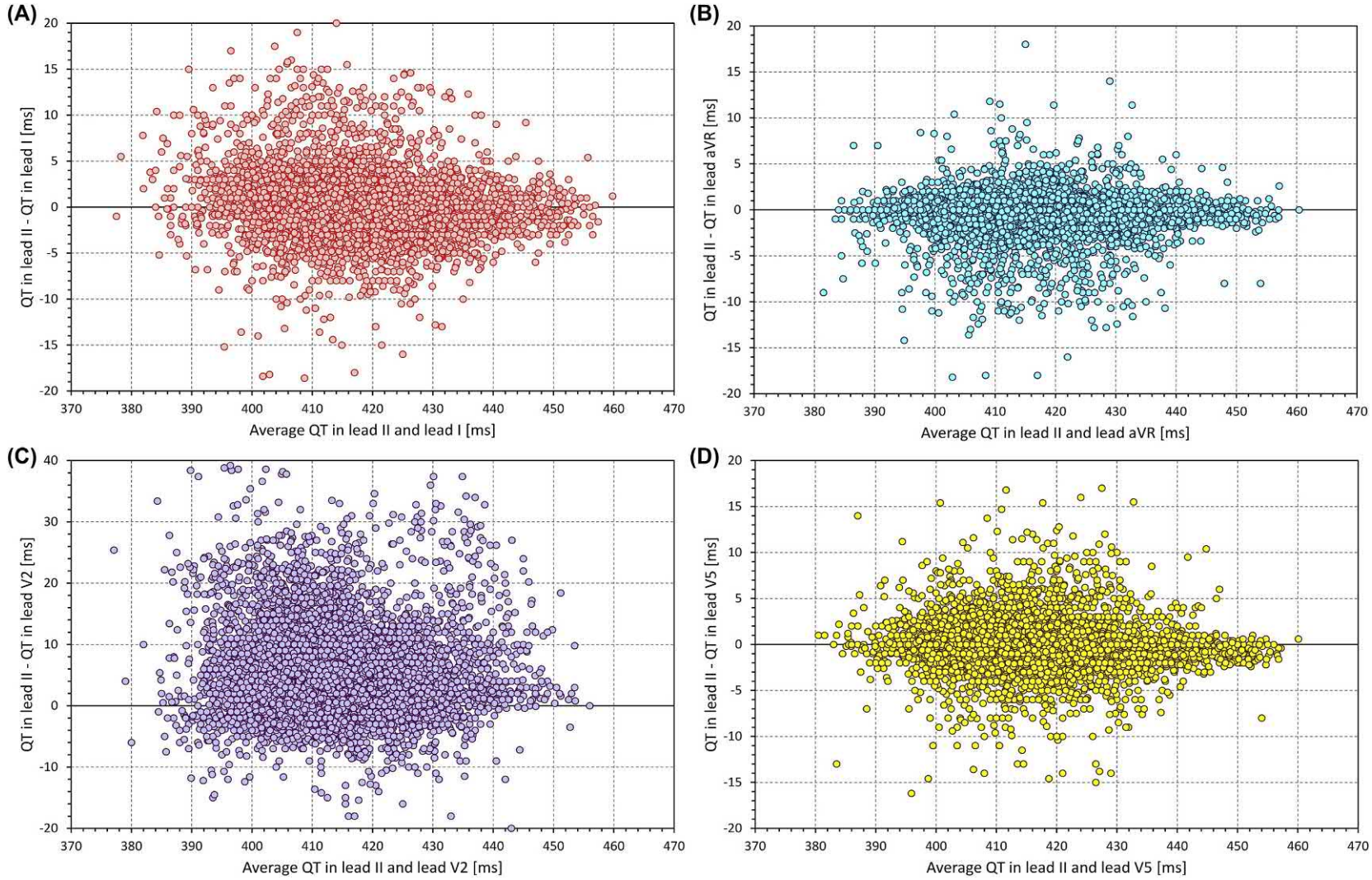

FIGURE 9.1 *QT* interval measurements in 8225 digital 12-lead ECGs obtained in healthy subjects: In each of the ECGs, *QT* intervals were measured (where measurable) in each lead by at least two independently working cardiologists with subsequent reconciliation of their differences. The figure shows the comparisons of *QT* interval durations measured in lead II with the measurements in other leads. Panels A, B, C, and D show scatter diagrams of the *QT* differences between lead II and leads I, aVR, V2, and V5, respectively, against the averages of the measurements in lead II and in the respective leads. *Reproduced with permission from Hnatkova K, Malik M. Sources of QTc variability: implications for effective ECG monitoring in clinical practice. Ann Noninvasive Electrocardiol 2020;25. https://doi.org/10.1111/anec.12730.*

Averaging of multiple measurements also enhances the accuracy. For ECG processing, this does not necessarily mean only averaging the separate measurements of the same lead in multiple QRS-T complexes. The averaging process can also be applied to the signals of properly aligned individual complexes to obtain the so-called representative QRS-T beatforms. When aligning the individual complexes and using sample-by-sample voltage medians rather than sample-by-sample averages, the process also filters the native recording and creates images that are easier to interpret. This is also true for recordings in which the *QT* interval measurement in individual beats is problematic because of underlying biological noise (Fig. 9.2), such as ECGs of patients with atrial fibrillation [12] or in Parkinson's disease patients [13]. The only exception in which this technology fails is fixed ratio atrial flutter with phase locked flutter waves and QRS complexes and with superimposition of flutter waves with the terminal part of the T wave.

When the representative beatforms of individual leads are displayed on the same isoelectric axis, comparison of the *QT* duration in different leads is also possible, further increasing the accuracy of the measurement. Measuring the *QT* interval in this so-called butterfly plot [14] appears more accurate compared to other possibilities.

While the identification of the QRS complex onset might occasionally be problematic, the difficulty of *QT* interval measurement stems mainly from the identification of the T-wave offset. The gradual transition of the downslope of the T wave into the isoelectric line or, perhaps more frequently, into the subsequent U wave makes any definition of the T-wave end highly dependent on the perception and interpretation of the ECG patterns. Unfortunately, neither human readers nor simple automatic systems are particularly accurate in maintaining the ECG interpretation constant and in measuring similarly shaped T waves consistently [15–17]. The inaccuracies caused by this inability to maintain the same interpretation approach to different ECGs might only occasionally be substantial and therefore call for the help provided by automatic algorithms that deal with the "systematicity" problem [15].

QT/heart rate hysteresis

Frequently, little attention is paid to the potentially substantial errors in *QTc* intervals due to incorrect heart rate measurements. That is, even if the *QT* interval is measured accurately, erroneous *QTc* values may be obtained if the *QT* interval duration is corrected for an *RR* interval that does not correspond to the heart rate that truly underlies the *QT* duration.

A most important source of these inaccuracies is the so-called *QT*/heart rate (or *QT*/*RR*) hysteresis. It has been repeatedly described that *QT* interval duration does not depend on (and thus should not be corrected for) instantaneously measured heart rate but that it responds to heart rate instability with a considerable delay [18–20]. This means that if *QT* interval is corrected for simultaneously measured *RR* interval while the heart rate is accelerating, erroneously long *QTc* value is obtained since the *QT* interval duration is still under the influence of the slower heart rate in the past. Correspondingly, if *QT* interval is corrected for simultaneously measured *RR* interval while the heart rate is decelerating, artificially short *QTc* value is produced.

Example of the problem is shown in Fig. 9.3, which shows two 10-s ECGs recorded in a healthy subject who was in a strict supine position for more than 5 min prior to the first ECG. These two tracings were separated by only a 10-s gap between them, and still, their heart rate differed by more than 20 beats per minute. The figure also shows that the uncorrected *QT* interval was the same as the time that elapsed between the two recordings was too short for the *QT* interval to adapt to the new or transient heart rate levels. When the *QT* interval was corrected for instantaneously measured 10-s heart rate, Bazett and Fridericia correction showed difference of 73 and 47 ms, respectively. However, when the 5-min heart rate history was used for individual *QT*/*RR* hysteresis correction (as described further), the corrected *QTc* intervals differed by only 2 ms.

Several ways to account for *QT*/*RR* hysteresis have been proposed [21–23]. All these proposals were based on formulas that process longer series of *RR* intervals preceding the *QT* interval measurement and, based on this history of *RR* interval development, produce a duration of *RR* interval that should be used for the correction of the *QT* interval [24,25].

Perhaps, most experience exists with the so-called exponential decay hysteresis model that is based on the following consideration: For a *QT* interval measurement, the sequence of preceding *RR* intervals $\{RR_i\}_{i=0}^{N}$ (RR_0 closest to the *QT* measurement) is considered. The *RR* interval representing the heart rate underlying the *QT* measurement is then calculated as

$$RR' = \sum_{i=0}^{N} \omega_i RR_i$$

where for each $j = 0, \ldots, N$,

$$\sum_{i=0}^{j} \omega_i = \left(1 - e^{-\lambda \frac{\sum_{i=0}^{j} RR_i}{\sum_{i=0}^{N} RR_i}}\right) / 1 - e^{-\lambda}$$

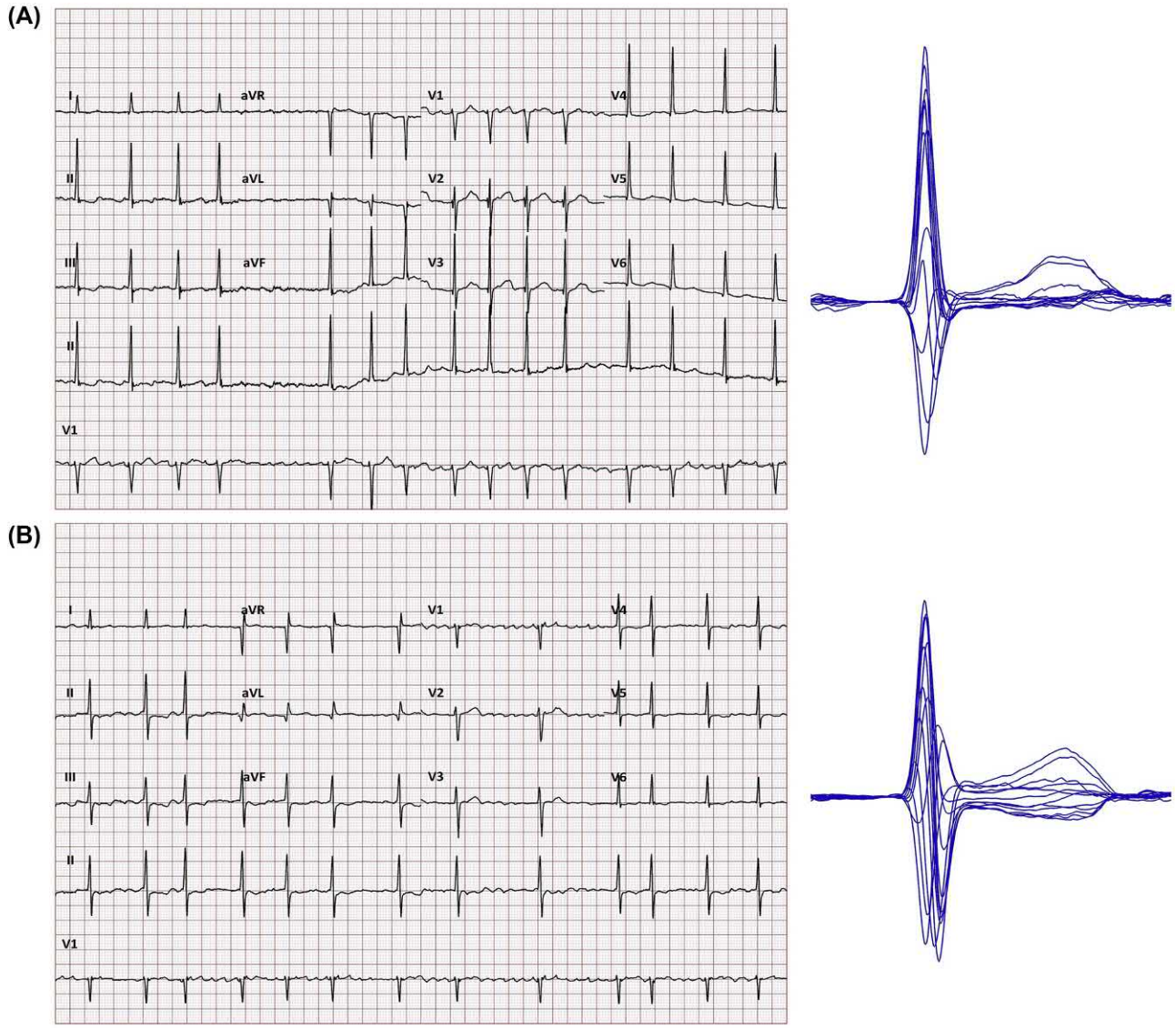

FIGURE 9.2 Digital 12-lead ECGs recorded in patients with atrial fibrillation ((A) 67-year old female, (B) 70-year old male). In both cases, any reasonably accurate *QT* interval measurement is clearly difficult if not impossible in the standard 12-lead printouts shown on the left-hand side. (Note that while T waves are visible in some of the precordial leads of both tracings, their morphology in individual beats is influenced by atrial fibrillatory waves that make the *QT* interval measurement inconsistent between individual cycles.) On the right-hand side, corresponding representative complexes are shown constructed with automatic determination of the QRS onset and superimposition of the segments preceding the QRS complex in all leads. While some noise due to the fibrillatory waves is still visible in the representative beatforms, *QT* interval duration can be made with sufficient confidence in both cases. *Reproduced with permission from Hnatkova K, Malik M. Sources of QTc variability: implications for effective ECG monitoring in clinical practice. Ann Noninvasive Electrocardiol 2020;25. https://doi.org/10.1111/anec.12730.*

The coefficient λ characterizes the subject-specific *QT*/*RR* hysteresis, i.e., the speed with which *QT* interval adapted to changing heart rate. To obtain the coefficient λ, multiple *QT* interval measurements at different heart rate and with different profiles of the *RR* interval history are needed. Subsequently, the coefficient λ is calculated by minimizing the spread of *QT*/*RR*′ values.

This principle is shown in Fig. 9.4, which shows scatter diagrams of *QT*/*RR* values obtained in two different healthy subjects in whom multiple *QT* interval measurements were made. The figure shows that relating the same *QT* interval durations to different expressions of *RR* intervals representing the underlying heart rate, the spread of the scatter diagrams is gradually reduced. When incorporating the hysteresis derived *RR*′ intervals, the individual-specific shape of the *QT*/*RR*′ relationship becomes compact and shows that there is little *QT* interval variability beyond the properly characterized heart rate influence.

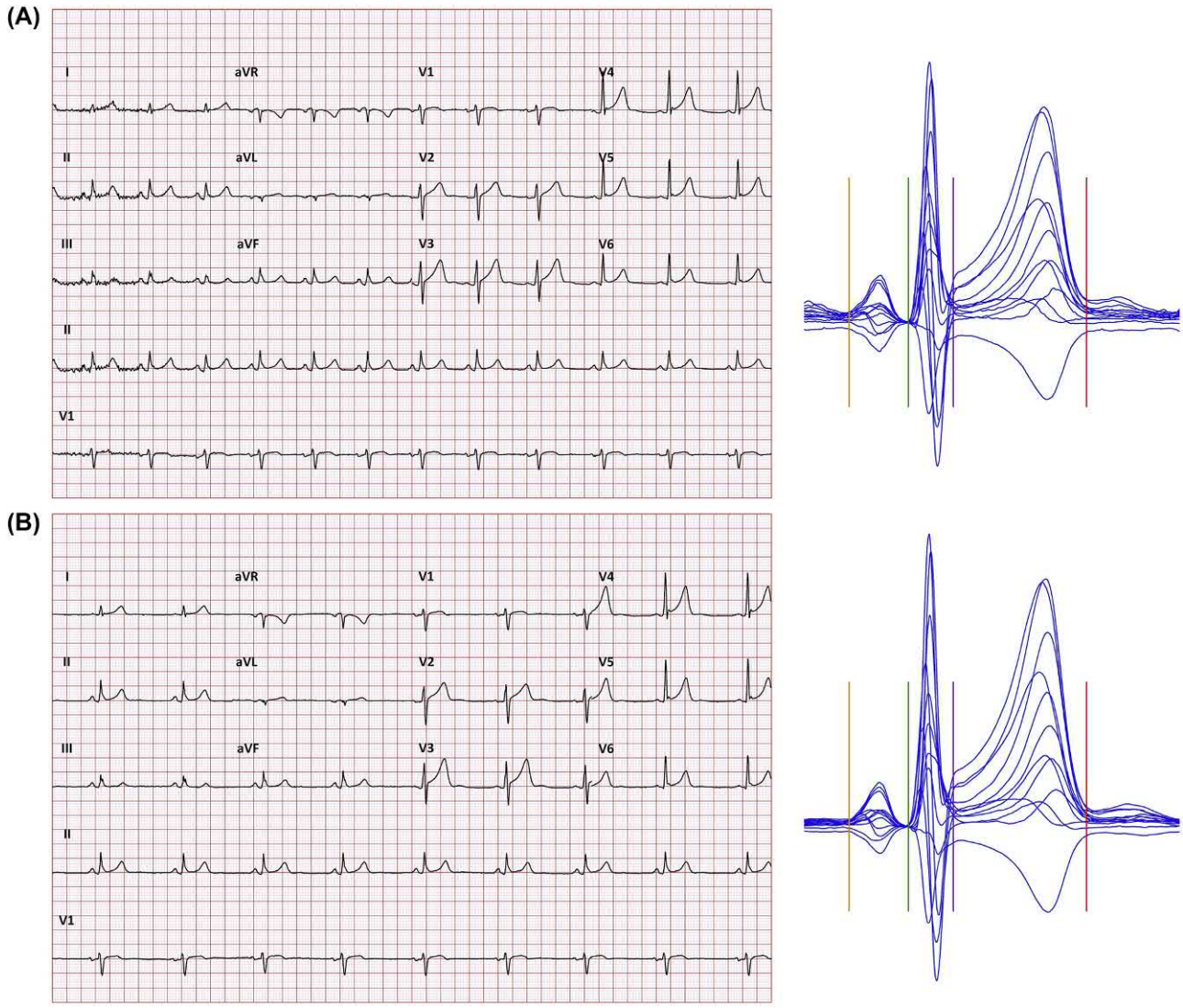

FIGURE 9.3 Digital 12-lead ECGs recorded in a 45-year-old healthy male off any medication. The recording A shown on the top started 20 s before the recording B shown on the bottom. The averaged 10-s heart rates were 73.5 and 53.4 beats per minute in recordings A and B, respectively. The images of representative beats of all 12 leads superimposed on the same isoelectric axis are shown on the right side of each panel. These also show the measurement triggers of P onset (amber line), QRS onset (green line), J point (violet line), and T offset (red line). The uncorrected *QT* interval in both tracings was the same 428 ms. When using the 10-s heart rate and correcting the *QT* interval by Bazett correction, *QTc* intervals of 474 and 403 ms were obtained. With Fridericia correction, the *QTc* values were 458 and 411 ms. When using individual correction that also involved individual *QT/RR* hysteresis component, *QTc* values of 417 and 419 ms were obtained. *Reproduced with permission from Hnatkova K, Malik M. Sources of QTc variability: implications for effective ECG monitoring in clinical practice. Ann Noninvasive Electrocardiol 2020;25. https://doi.org/10.1111/anec.12730.*

Since the value of λ represents the speed with which the *QT* interval duration adapts, it is customary to convert it into the so-called hysteresis time constant, i.e., the time needed for the *QT* interval to reach 95% of its new value after a heart rate change.

Similar to fixed heart rate corrections, it was also proposed that universal hysteresis correction is possible allowing to correct for hysteresis without optimizing the coefficient λ in each subject separately. Since, in healthy subjects, the 95% adaptation of the *QT* interval after heart rate changes is on average achieved after 2 min, the hysteresis correction model with $\lambda = 7.4622$ (which corresponds to the 2-min 95% adaptation) may be used universally in physiologic studies [26]. In cardiac patients, however, different hysteresis correction models are needed [27].

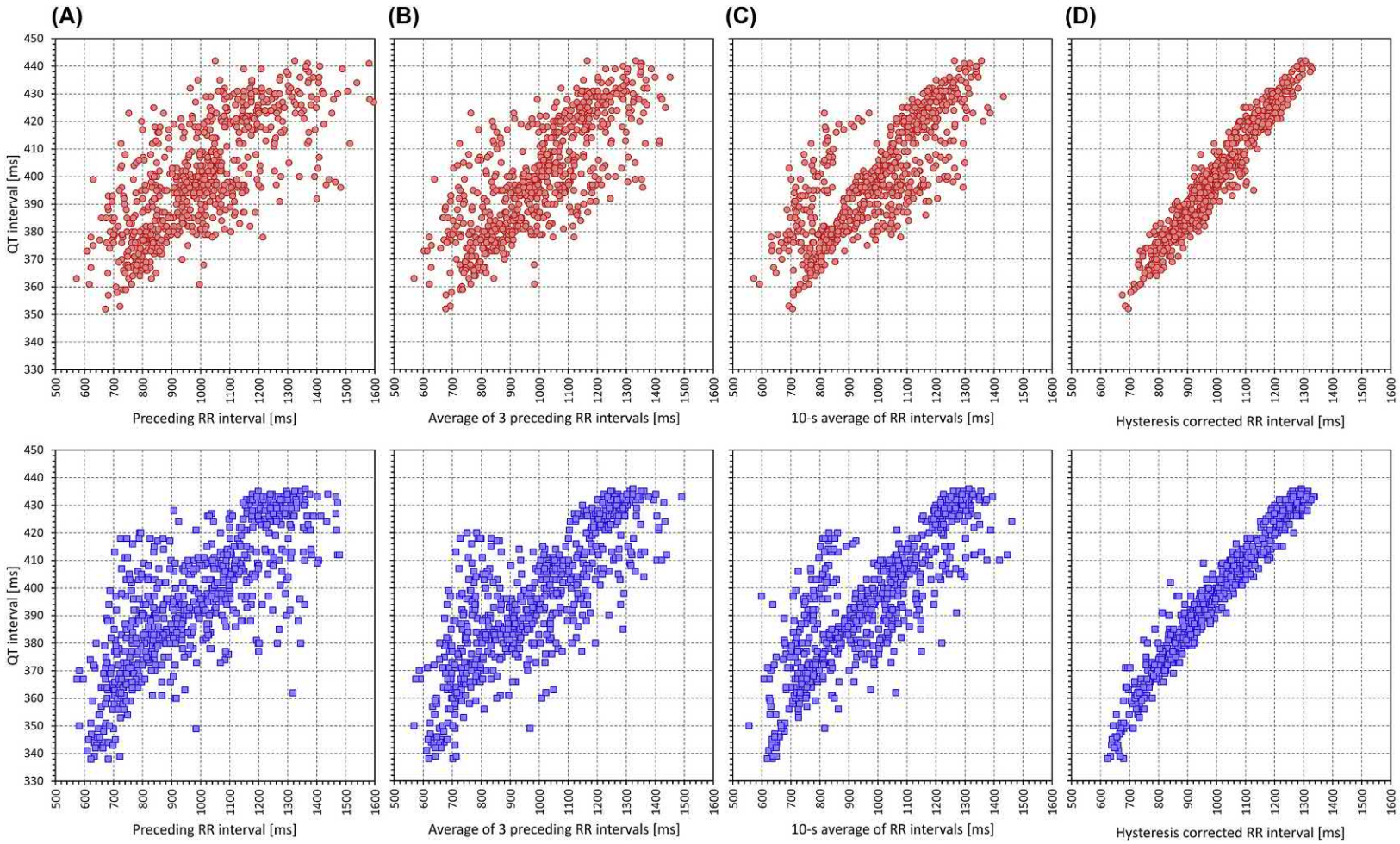

FIGURE 9.4 Examples of the relationship of repeated *QT* measurements to different *RR* interval expressions. The top row shows data obtained in a 22-year-old healthy female in whom *QT* interval was measured in 719 different extractions from daytime long-term 12-lead ECGs; the bottom row shows data obtained in a 27-year-old healthy male in whom *QT* interval was measured in 720 different extractions from daytime long-term 12-lead ECGs. In each of these two subjects, the same *QT* interval durations (measured at different underlying heart rates) were related to the durations of the *RR* intervals immediately preceding the *QT* measurement (left most panels A), to the averages of three *RR* intervals preceding the *QT* measurements (panels B), to the averages within the 10-s ECG segment in which the *QT* interval measurement were made (panels C), and to the *RR* interval durations obtained by the subject-specific hysteresis correction applied to the 5-min series of *RR* intervals preceding the *QT* interval measurement (rightmost panels D). Note that the variability of the scatter diagrams gradually decreases from A to D with the most suppression of the variability in the step from C to D.

Intrasubject stability of *QT*/heart rate profiles

It has repeatedly been described that *QT*/*RR* patterns show tight intrasubject reproducibility while also showing intersubject variability [28,29]. The intrasubject stability of the pattern exists not only in healthy subjects but has also been observed in populations of noncardiac patients [13], while in cardiac patients, the *QT*/*RR* relationship has been reported to provide risk assessment [30,31].

Figs. 9.5 and 9.6 show that the intrasubject *QT*/*RR*′ stability and intersubject variability exists in both sexes. Similar to other publications, these figures show the intrasubject stability over the period of some months. Nevertheless, similar intrasubject reproducibility and intersubject differences have also been observed over a longer period of approximately 2 years [32].

Assessment of sex differences in population data

To document the sex differences in *QTc* interval and in other characteristics of the *QT*/*RR* relationship, subsequent sections of this chapter present analyses of ECG data obtained in 335 healthy females (aged 34.5 ± 10.3 years) and 416 healthy males (aged 34.2 ± 8.7 years) with no statistically significant age differences between the sex groups. All these subjects were investigated in different ethically approved and individually consented clinical pharmacology studies. All subjects had normal clinical screening ECG and passed inclusion health checks relevant to clinical pharmacology investigations [33]. All the source studies obtained multiple daytime 12-lead Holter recordings, while the subjects were not on any medication. During these recordings, the investigated subjects also did not smoke and were not allowed to consume any alcohol or caffeinated drinks.

Using previously published methods [13,34], QRS onset and T-wave offset were identified in multiple samples taken from the 12-lead Holter recording. The measurements were made in representative morphologies derived from 10-s ECG segments and were sampled at 1000 Hz. Previously reported pattern matching algorithms [15] were also used to ensure that similar morphologies of the QRS onset and offset and of T-wave offset were measured similarly. Quality control of the measurements included visual verification and manual correction of computerized measurements by at least two independently working cardiologists with data reconciliation in cases of their disagreement. Multiple measurements were made in each Holter recording while the subjects were in supine position and during free daily activity that included postural provocations. This led to substantial heart rate spans in each subject [34]. For each measured ECG sample, a 5-min history of *RR* intervals preceding the measurements was also obtained. To avoid influences of sleep, all the measurements were made during periods when the subjects were fully awake.

In each subject of this population of healthy subjects, 321−1560 *QT* interval measurements were made (median 1396 and 1298 *QT* measurements in females and males, respectively; no significant difference between the sex groups).

Shape of *QT*/*RR* profiles

When the individual *QT* interval measurements were related to the corresponding hysteresis-corrected *RR*′ intervals, the individual-specific patterns were not differently steep (see the comparisons of cases in Figs. 9.5 and 9.6), which corresponded well to previous observations [28,29]. To demonstrate the spreads of the patterns, five different regression models were fitted to the *QT* and *RR*′ (hysteresis-corrected) data of each subject:

(a) Parabolic (log/linear) model in the form $QT = \omega \times RR^{\alpha}$, which leads to a heart rate correction form $QTc = QT/RR^{\alpha}$, i.e., to a generalized form of the Bazett [35] ($QTc = QT/RR^{0.5}$) and Fridericia [36] ($QTc = QT/RR^{1/3}$) corrections,

(b) Linear model in the form $QT = \omega + \beta \times RR$, which leads to a heart rate correction form $QTc = QT + \beta \times (1 - RR)$, i.e., to a generalized form of the Framingham correction formula [37] ($QTc = QT + 0.154(1 - RR)$),

(c) Hyperbolic model in the form $QT = \omega + \xi/RR$, which leads to heart rate correction form $QTc = QT + \xi \times \left(\frac{1}{RR} - 1\right)$, i.e., to a generalized form of the Hodges correction formula [38] ($QTc = QT + 0.00175(HR - 60)$),

(d) Logarithmic model $QT = \omega + \varphi \log(RR)$, which leads to a heart rate correction form $QTc = QT - \varphi \log(RR)$, and

(e) Exponential model $QT = \omega + \phi \times e^{-RR}$, which leads to a heart rate correction form $QTc = QT + \phi \times (e^{-RR} - 1/e)$.

where the *QT*, *RR*, and *QTc* values are in seconds, *HR* is heart rate in beats per minute, e is the base of natural logarithms, and in all the models, ω represents the intercept value.

The purpose of *QT* heart rate correction is to eliminate the effect of underlying heart rate (i.e., the hysteresis-corrected *RR* interval) on the *QTc* duration. Hence, the optimum subject-specific setting of a heart rate correction

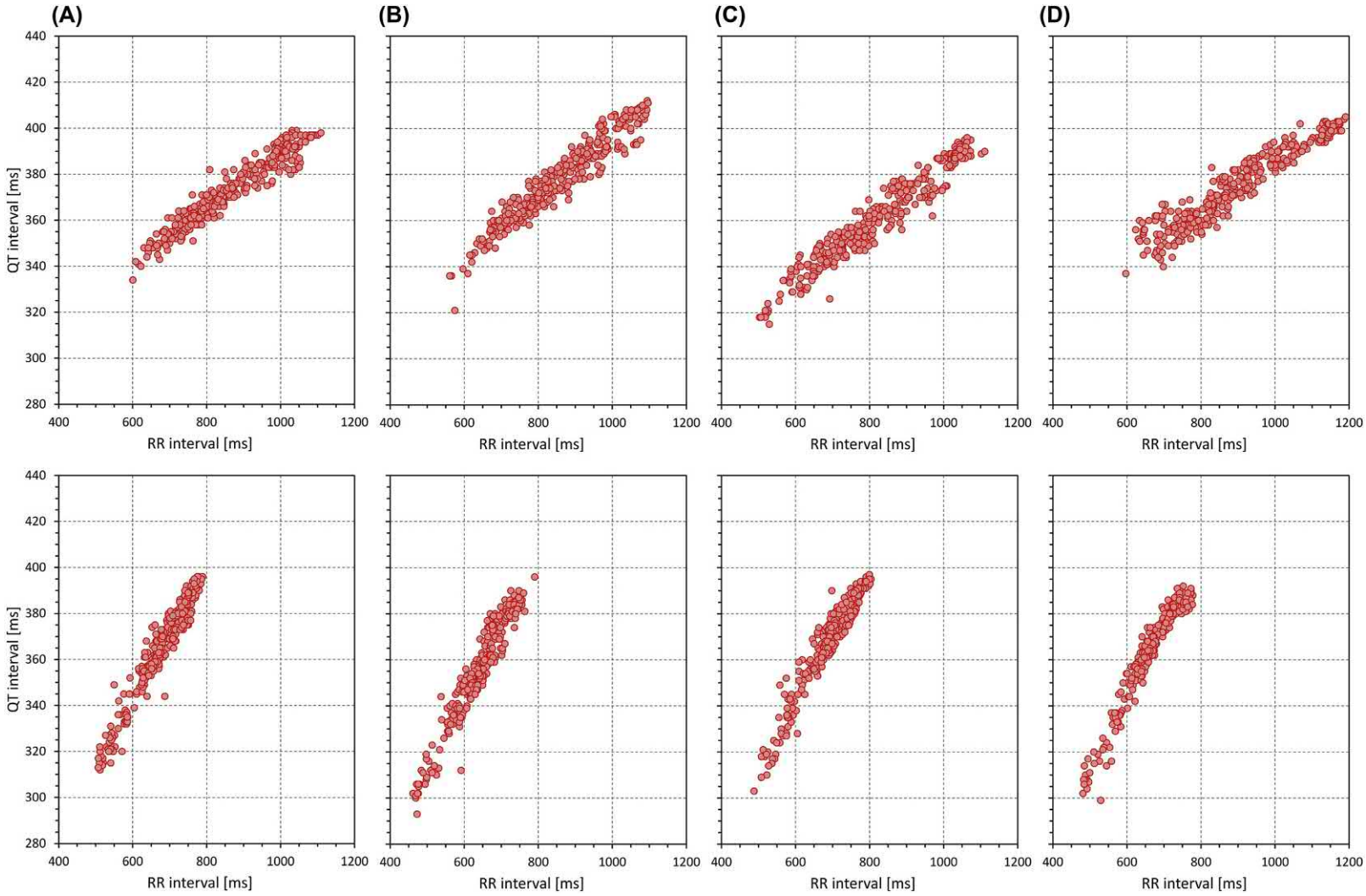

FIGURE 9.5 Examples of intrasubject stability and intersubject differences in two female subjects. The top and bottom panels show data obtained in a 45-year-old healthy female and a 39-year-old healthy female, respectively. In both these subjects, *QT* measurements were made in four different daytime 12-lead Holter recordings spanning approximately over a 1 month. In the female shown on the top, 359, 359, 360, and 360 *QT* interval readings were made (at different underlying heart rates) in the different Holter recordings. In the female shown at the bottom, the corresponding numbers of *QT* readings in different Holters were 311, 316, 343, and 333. The panels of the figure show the relationship of the measured *QT* intervals to the *RR* intervals obtained by the means of individual hysteresis correction. The panels A, B, C, and D correspond to different Holters. Note that while the *QT*/*RR* profiles are very different between the two cases, they are closely reproduced between different recordings days in the same subject. Compare also with Fig. 9.6.

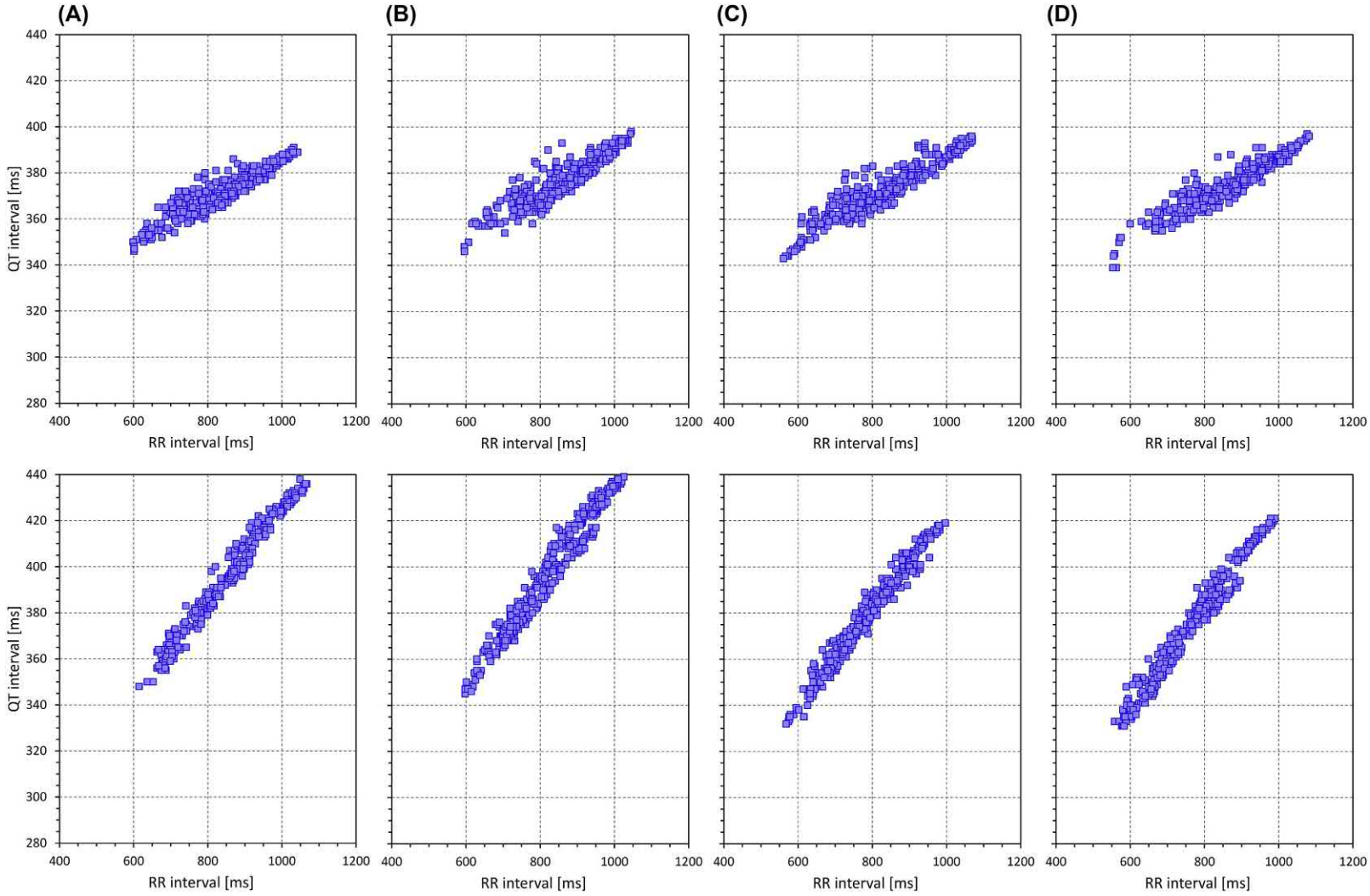

FIGURE 9.6 Examples of intrasubject stability and intersubject differences in two male subjects. The top and bottom panels show data obtained in a 46-year-old healthy male and a 38-year-old healthy male, respectively. In both these subjects, *QT* measurements were made in four different daytime 12-lead Holter recordings spanning approximately over 1 month. In the male shown on the top, 357, 360, 360, and 358 *QT* interval readings were made (at different underlying heart rates) in the different Holter recordings. In the male shown at the bottom, 360 separate *QT* readings were made during each of the four different Holters. The panels of the figure show the relationship of the measured *QT* intervals to the *RR* intervals obtained by the means of individual hysteresis correction. The panels A, B, C, and D correspond to different Holters. Note that while the *QT*/*RR* profiles are very different between these two cases, they are closely reproduced between different recording days in the same subject. Compare also with Fig. 9.5.

is by finding the correction coefficient which, in the given subject, leads to zero correlation between QTc values and RR' values. (Note that this holds true for each subject separately. Applying the same principle to pooled population data may lead to substantial bias and erroneous estimates [39]).

Fig. 9.7 shows the dependencies of QTc versus RR' correlations on the correction parameters of individual optimization coefficients for the parabolic, linear, and hyperbolic correction formulas. The panels of the figure show separate lines for individual healthy subjects of the population used here for the demonstration of the principles. The figure shows not only that different subjects differ very substantially in the optimum setting of the correction coefficients but also that there are substantial sex differences in these settings. While the numerical settings of Fridericia, Framingham, and Hodges formulas are approximately in the middle of the spread of the male population, this is not the case for the female population.

Moreover, the different regression models differ also in the closeness of the fit of the QT/RR' data in individual subjects. This can be studies by the intrasubject standard deviations of QTc values obtained by the means of different individually optimize formulas. Fig. 9.8 shows that when the "best" formula of the five possibilities (i.e., the formula which, when individually optimized with zero correlation between QTc and RR', led to the smallest standard deviation of QTc values) was identified for each subject, the spread of the "best" formulas differed substantially between females and males. While in approximately 50% of males, linear formula was fitting the data better than the other possibilities, logarithmic formula was found to be the "best" possibility among females more frequently than the other investigated forms. This corresponds well to previous observations [41].

These comparisons lead to the observation that the QT/RR' pattern is, on average, not only differently steep in females and males but that it also shows sex difference in the extent of the nonlinearity of the QT/RR' relationship, that is a sex difference in the QT/RR' curvatures.

Note also that the parabolic form that became somewhat popular in different populations was also among the possibilities that lead least frequently to the best fit of the QT/RR' data [40].

Curvilinear QT/RR modeling

The interindividual differences in the QT/RR curvature led to the technology of using curvilinear models to describe the subject-specific QT/RR profiles. Specifically, regression QT/RR' models were investigated using the regression equation $QT = \omega + \varphi \times (RR^{\gamma} - 1)$, which leads to the generic correction form $QTc = QT + \frac{\delta}{\gamma}(1 - RR^{\gamma})$ [42], where QT, QTc, and RR are again in seconds, γ is the parameter of the curvature of the relationship (the smaller the value, the more concave the QT/RR' profile), and δ is the slope of the curvilinear relationship (the fraction δ/γ is used in the correction equation for simple mathematical reasons [42]).

Fig. 9.9 shows the comparison of different characteristics of the subject-specific curvilinear QT/RR' models (all the sex differences shown in the figure are statistically significant). It can be seen that when the hysteresis profiles were optimized together with the curvilinear models, the time constants were marginally shorter in females compared to males (i.e., females adapted the QT interval duration to heart rate changes marginally faster compared to males). Consistent with the observation already shown in Fig. 9.8, the QT/RR' profiles were more curved in females compared to males, and the QT/RR' patterns were substantially steeper in females than in males. (Fig. 9.9 shows the slopes of the linear and parabolic models that are easier to interpret compared to the slopes of the curvilinear models. Nevertheless, the same sex difference was also observed with the curvilinear models.) This all is in full agreement with previously published observations [42,43].

Accuracy of QTc corrections

All these observations have profound implications for the accuracy of heart rate corrections of the QT interval. As already mentioned, providing that there are no pharmaceutical or pathology-related reasons for the QTc interval to change, the accuracy of different heart rate corrections may be assessed by calculating standard deviation of repeated QTc measurements in the same individual. This concept is based on the observation that in healthy subjects who are not on any repolarization active drug, daytime recordings show little QTc variability [44].

Fig. 9.10 shows the cumulative distributions of intrasubject standard deviations of repeated QTc values obtained in the population described as above when Bazett, Fridericia, Framingham, and Hodges corrections were used to calculated QTc values using the averages of RR intervals from the 10-s ECG segments in which the QT interval measurements were made. The figure shows that with this approach to the correction, the QTc variabilities were substantial, especially with the Bazett correction. It also shows that in these cases, the variabilities were marginally lower in females compared

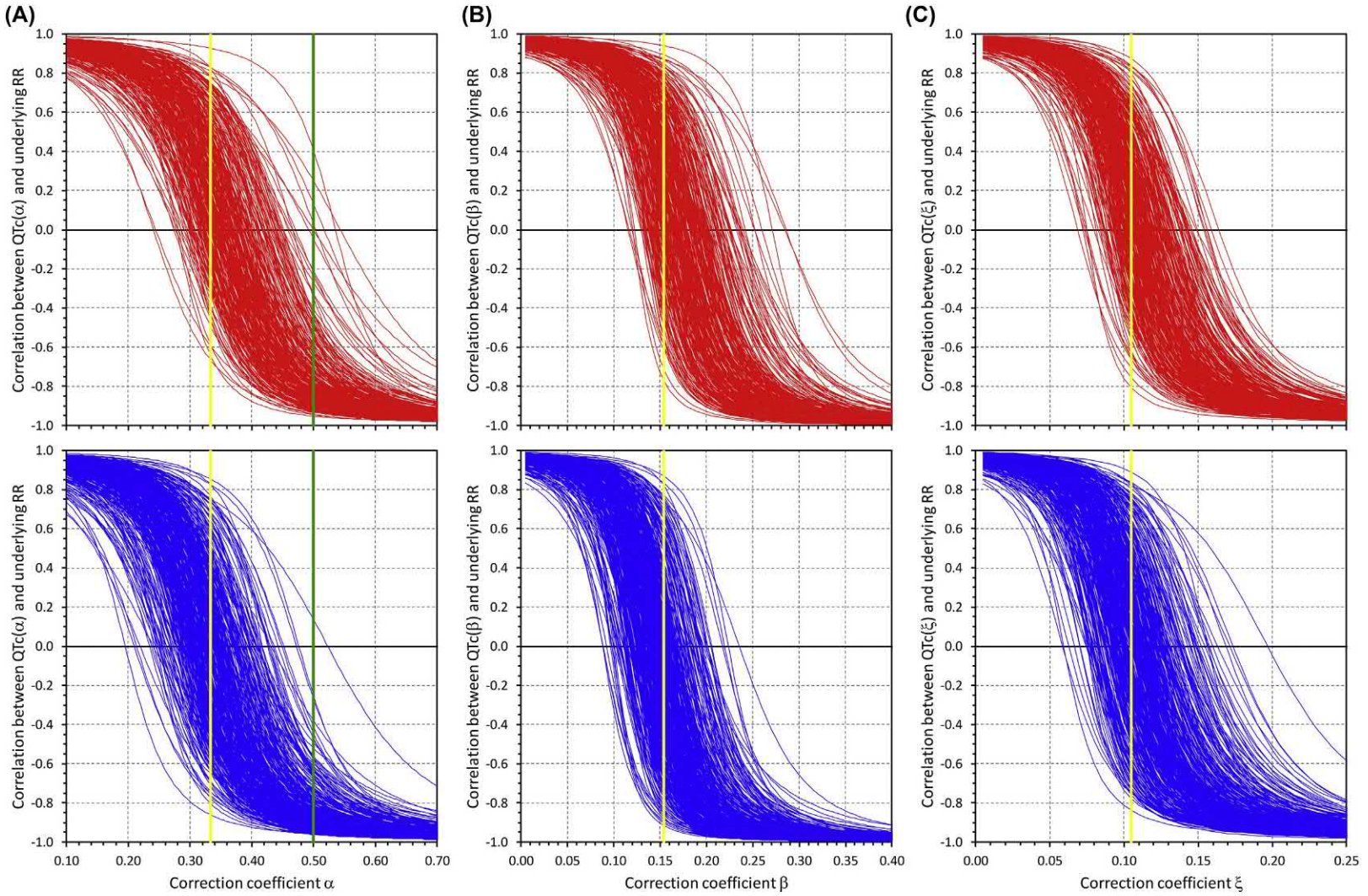

FIGURE 9.7 For different subjects of the healthy population (see the text for details), the panels A show the Pearson correlation coefficients between RR' intervals (obtained with subject-specific hysteresis corrections) and the corresponding values $QTc(\alpha) = QT/RR^{\alpha}$ as dependent on the value of correction parameters α. The panels B show the same for $QTc(\beta) = QT + \beta \times (1 - RR)$ and correction parameters β. The panels C show the same for $QTc(\xi) = QT + \xi \times \left(\frac{1}{RR} - 1\right)$ and correction parameters ξ. The panels on the top show the results in female subjects, and the panels at the bottom show the results in male subjects. Note that in different subjects, zero correlation between *RR* intervals of the underlying heart rate and the *QTc* intervals is obtained with very different correction parameters. The yellow and green vertical lines in panels A correspond to the Fridericia and Bazett correction formulas, the yellow vertical lines in panels B to the Framingham correction formula, and the yellow vertical lines in panels C to the Hodges correction formula (note that the original form of the Hodges formula uses heart rate rather than *RR* interval duration—appropriate recalculation was made). The figure not only shows that different subjects need different correction parameters but also that the results of fixed corrections are unpredictable in different subject—for instance, while Fridericia formula was close to the center of individual settings of correction coefficients in the male population, there were subjects in whom the Fridericia corrected *QTc* values were highly positively correlated with underlying *RR* values while other subjects in whom these values were highly negatively correlated. The same applied to Framingham and Hodges formulas.

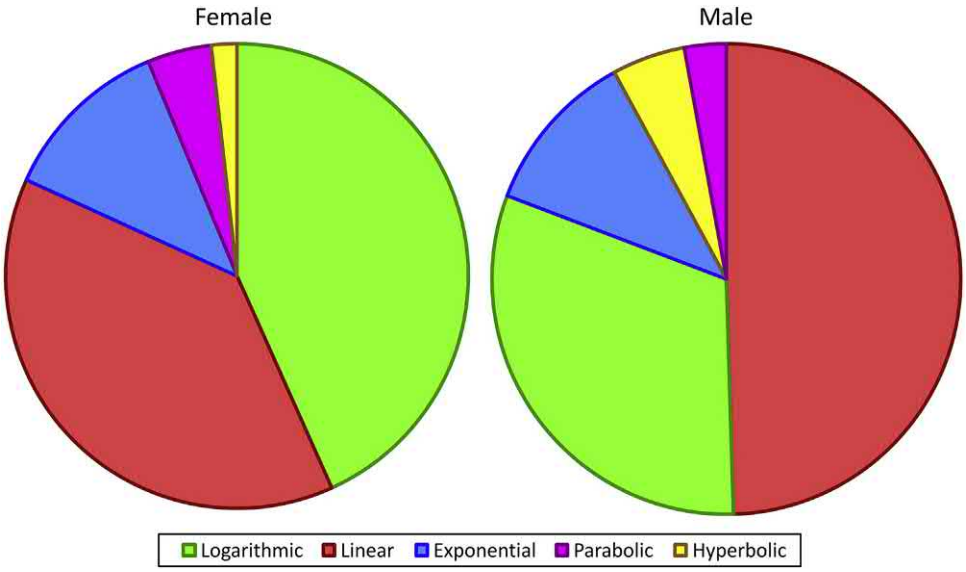

FIGURE 9.8 Pie charts of the population distribution of different regression models that led to the lowest intrasubject standard deviations of *QTc* values. For both sexes, the pie chart is ordered clockwise from the most to the least frequent cases.

to males. The large values of *QTc* standard deviations are not surprising when considering the wide spreads of corresponding intrasubject *QT*/*RR* scatters shown in Fig. 9.4 (the data shown in Fig. 9.10 correspond to the panels second from the right in Fig. 9.4). Fig. 9.4 also suggests that when the intrasubject spreads of *QTc* values are calculated using the correction of *QT* durations for the immediately preceding *RR* intervals, the variability of *QTc* data is even larger. This is indeed the case.

Fig. 9.10 contrasts with Fig. 9.11 in which the distributions are shown for the intrasubject standard deviations of *QTc* obtained when combining the same correction formulas with the hysteresis-corrected *RR′* interval values. As seen (and as it corresponds to the graphics comparisons in Fig. 9.4), the intrasubject standard deviations more than halve by this switch to a more physiologically realistic expression of *RR* interval representing the heart rates that influence the *QT* interval duration. Fig. 9.11 also shows that the sex comparisons change with the more accurate *QTc* assessment since in Fig. 9.10, the spread of intrasubject *QTc* values was also influenced by the intrasubject variations of heart rates that were also different between the sexes. Moreover, the accuracy of the corrections was also influenced by the sex-related bias of the evaluated corrections as already noted in Fig. 9.7.

Application of the individually optimized curvilinear corrections reduces the intrasubject variability of *QTc* values even further as shown in Fig. 9.12. This figure shows that when most of the heart rate influence of the *QT* interval duration, including the influence of heart rate variability, is removed by the curvilinear regression models combined with intrasubject hysteresis correction, the intrasubject *QTc* variability becomes marginally albeit statistically significantly larger in females compared to males.

Sex differences of *QT* interval durations

Since the *QTc* interval values and *QT*/*RR′* profiles obtained by the means of the subject-specific curvilinear corrections are more accurate compared to other *QTc* variants, they are suitable for an accurate assessment of sex differences of the *QTc* interval duration and of the *QT*/*RR′* dependency.

The difference between females and males is shown in Fig. 9.13. This figure demonstrates that as a consequence of the sex differences in the *QT*/*RR′* slopes and curvatures, the *QT* difference between sexes depends on the underlying heart rate. At resting heart rate of 60 beats per minute, the cumulative distribution of the *QT* values (and thus of the individual *QTc* values) in females shows an almost 20 ms constant shift toward longer values. This means that the 20 ms difference is seen not only between the *QTc* medians in females and males but also between the upper and lower quartiles, upper and lower 90th percentiles, etc., despite some overlap between the *QTc* values in both sexes (note in Fig. 9.13 that, for instance, approximately 25% of males have *QTc* interval longer than the lower *QTc* quartile in females).

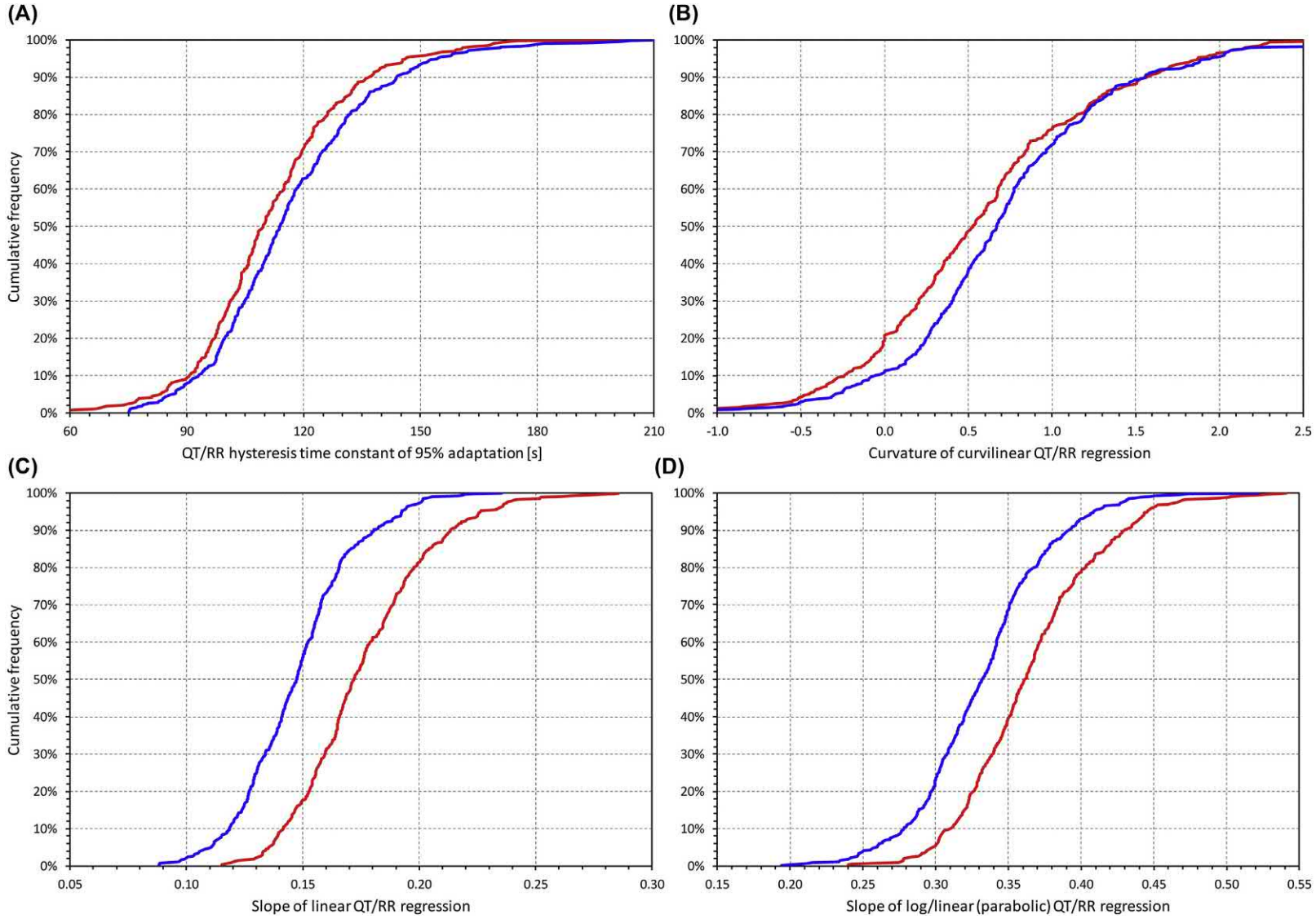

FIGURE 9.9 Cumulative distributions of the characteristics describing the subject-specific *QT*/*RR*′ patterns. Panel A shows the distributions of hysteresis time constants, panel B of the curvature coefficients of the curvilinear *QT*/*RR*′ regression models, panel C of the slope of the linear *QT*/*RR*′ regressions, and panel D of the slope of the log/linear (parabolic) *QT*/*RR*′ regressions. In each panel, the red and blue lines correspond to the cumulative distributions of the data in female and male subjects, respectively.

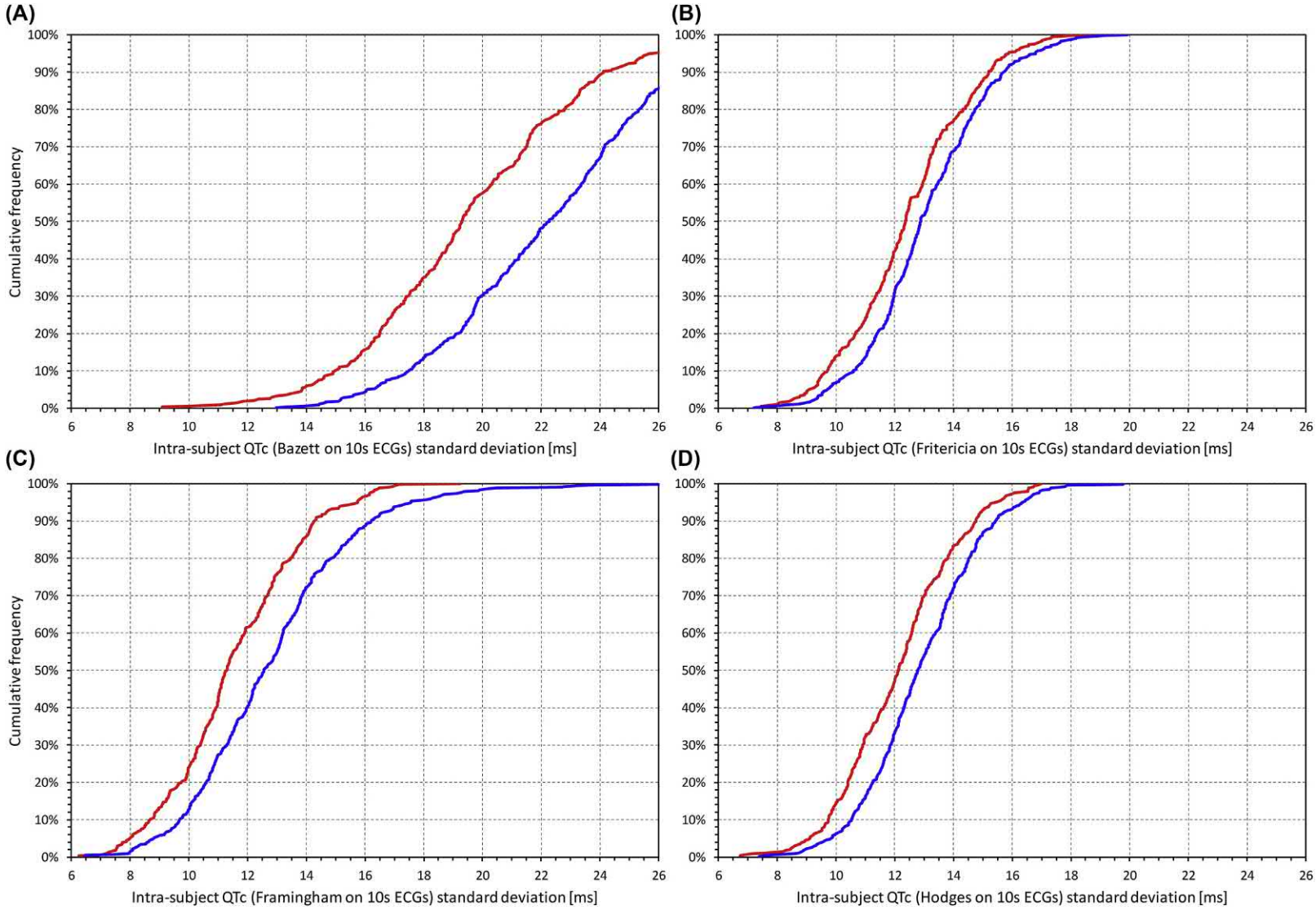

FIGURE 9.10 Cumulative distributions of intrasubject standard deviations of *QTc* values obtained with Bazett (panel A), Fridericia (panel B), Framingham (panel C), and Hodges (panel D) heart rate correction used to correct the measured *QT* intervals for the averages of *RR* intervals in the 10-s ECG segments in which the *QT* intervals were measured. In each panel, the red and blue lines correspond to the cumulative distributions of the data in female and male subjects, respectively. Compare to Figs. 9.11 and 9.12.

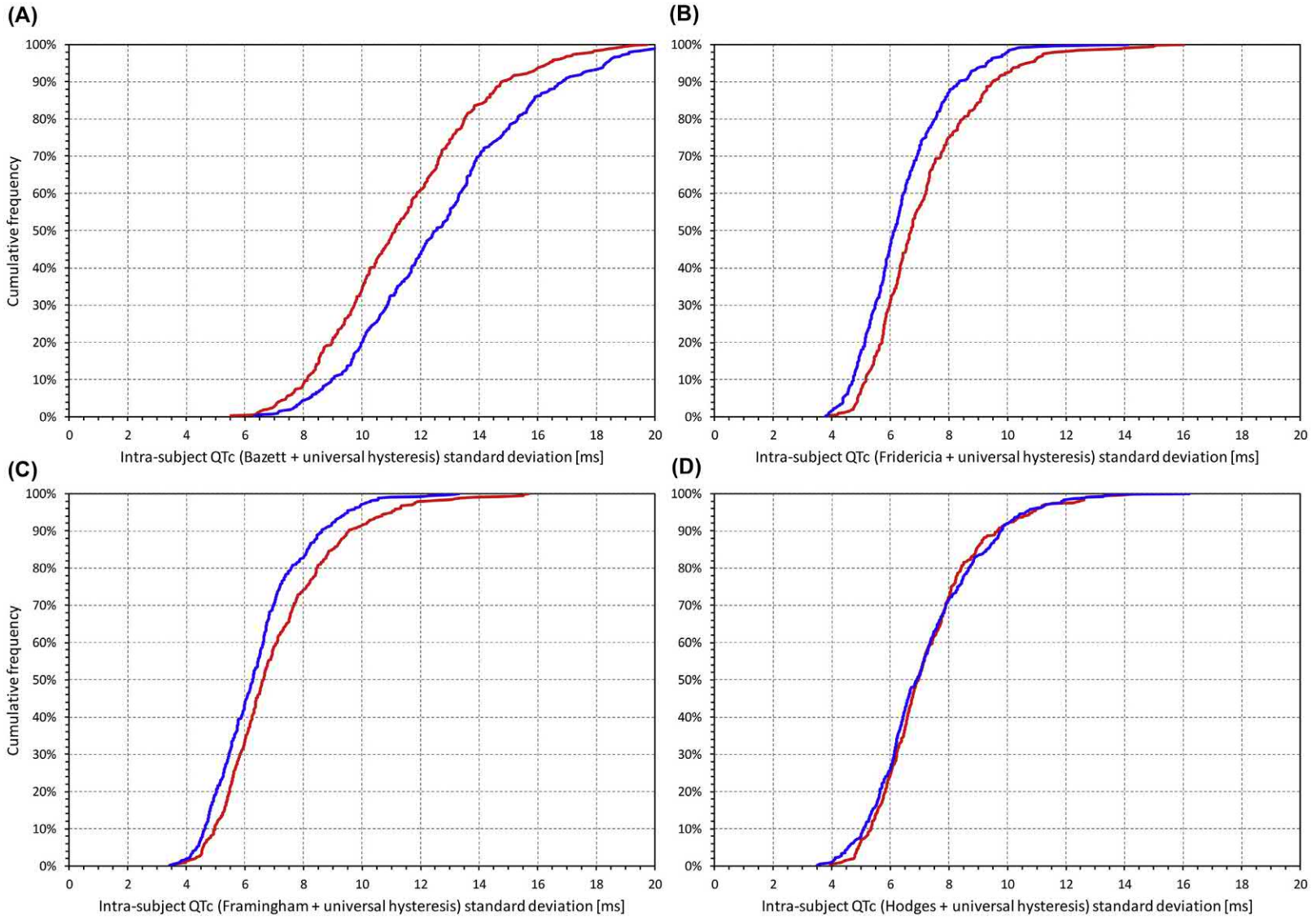

FIGURE 9.11 Cumulative distributions of intrasubject standard deviations of *QTc* values obtained with Bazett (panel A), Fridericia (panel B), Framingham (panel C), and Hodges (panel D) heart rate correction used to correct the measured *QT* intervals for the averages of RR' intervals obtained by the means of the universal *QT*/*RR* hysteresis correction. In each panel, the red and blue lines correspond to the cumulative distributions of the data in female and male subjects, respectively. Compare to Figs. 9.10 and 9.12.

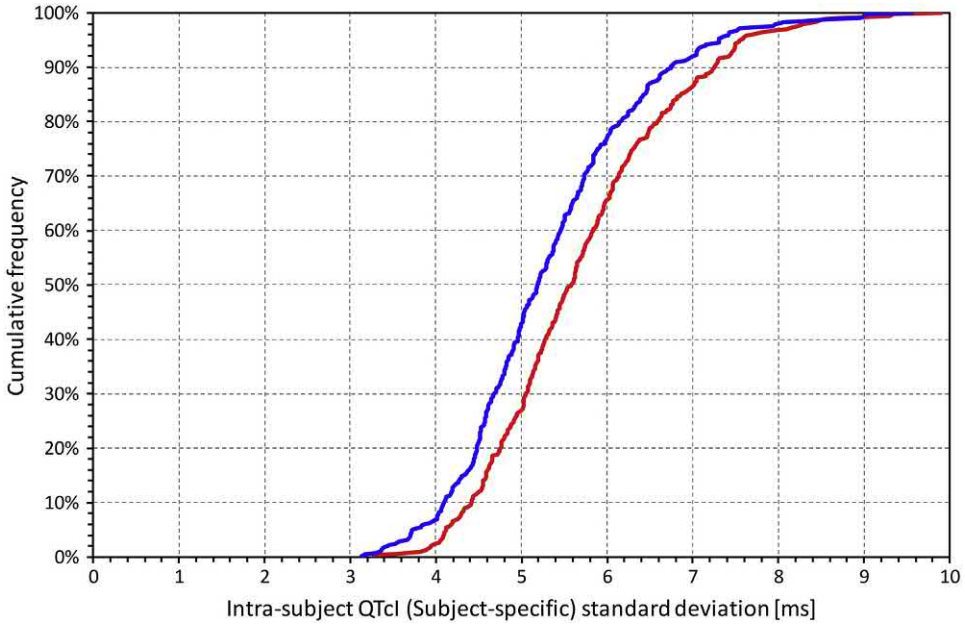

FIGURE 9.12 Cumulative distributions of intrasubject standard deviations of *QTc* values obtained with subject-specific curvilinear heart rate correction combined with subject-specific hysteresis corrections (*QT*cI intervals). The red and blue lines correspond to the cumulative distributions of the data in female and male subjects, respectively. Compare to Figs. 9.10 and 9.11.

With increasing heart rate, the sex difference diminishes. When assessing the *QTc* interval at the heart rate of 90 beats per minute, the initial 20 ms difference is reduced to about 10 ms, while at the heart rate of 120 beats per minute, it is reduced further to approximately 5 ms (although at this heart rate, the cumulative distributions of the *QT* values in females and males are no longer parallel).

Influence of age

Previously, it has been described that *QTc* interval increases with increasing age [1]. Similar effect is seen in Fig. 9.14 that also shows gradual age-related increases in the *QTc* values (obtained with individual curvilinear models and individual hysteresis correction). Nevertheless, the increases observed with this correction technology were less marked compared to earlier publication suggesting that the previously used simpler *QT* measurement and *QTc* correction technologies might have been influenced by heart rate changes that are known with advancing age.

Fig. 9.14 also shows that the *QT*/*RR* hysteresis time constant gradually increases with age. This suggests that the mechanisms of the hysteresis are controlled by autonomic nervous system that is known to decrease its tone and modulations with advancing age.

The *QT*/*RR*′ curvatures were not found to be age dependent, and only a shallow trend toward a decrease of *QT*/*RR*′ slopes with advancing age was noted.

Conclusion

In summary, the presented analyses show several aspects of sex differences related to the *QT* interval duration and to its rate relationship. Compared to males, females have longer *QT* interval duration especially at slow heart rates while with increasing heart rates, the sex difference in *QT* duration diminishes. Females also adapt the *QT* interval to changing heart rate marginally faster than males and have the *QT*/*RR* profiles more curved and steeper than males.

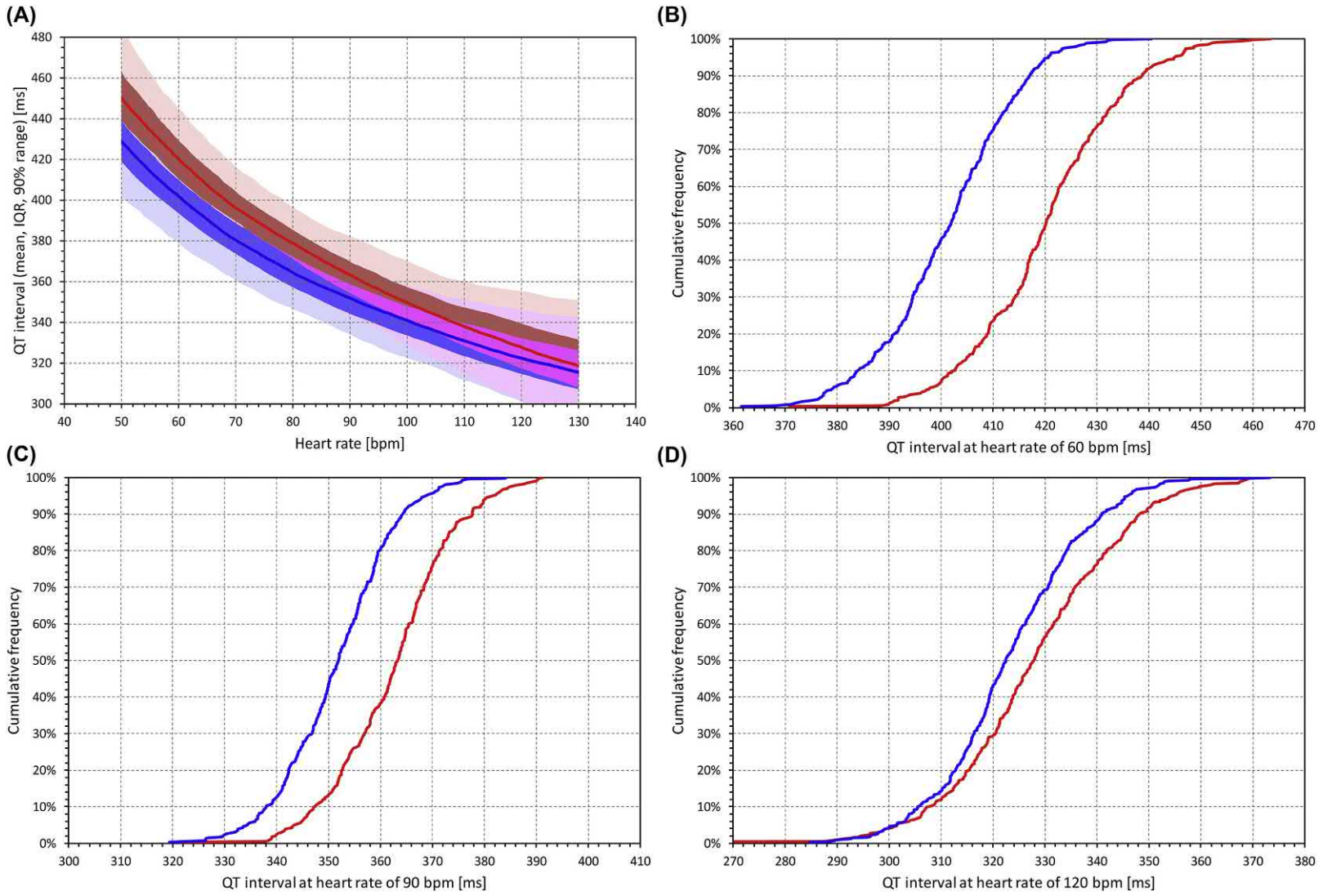

FIGURE 9.13 Panel A shows the population data of the heart rate influence on the *QT* interval duration obtained by the means of subject-specific curvilinear heart rate correction combined with subject-specific hysteresis corrections. For different heart rate levels, the bold red and blue lines show the median *QT* interval durations among female and male subjects, respectively. The dark-red shaded and dark-blue shaded areas show the interquartile ranges of the *QT* intervals among female and male subjects, respectively. The dark-violet shaded areas show the values for which the female and male interquartile ranges of *QT* intervals overlap. The light-red shaded and light-blue shaded areas show the ranges between the 10th and 90th percentile of the *QT* intervals among female and male subjects, respectively. The light-violet shaded areas show the values for which the female and male 10th−90th percentile ranges of *QT* intervals overlap. Panels B, C, and D show cumulative distributions of *QT* intervals at heart rates of 60, 90, and 120 beats per minute (bpm), respectively. (Note that the *QT* values at the heart rate of 60 beats per minute represent the individually corrected *QTc* values). In panels B, C, and D, the red and blue lines correspond to the cumulative distributions of the data in female and male subjects, respectively.

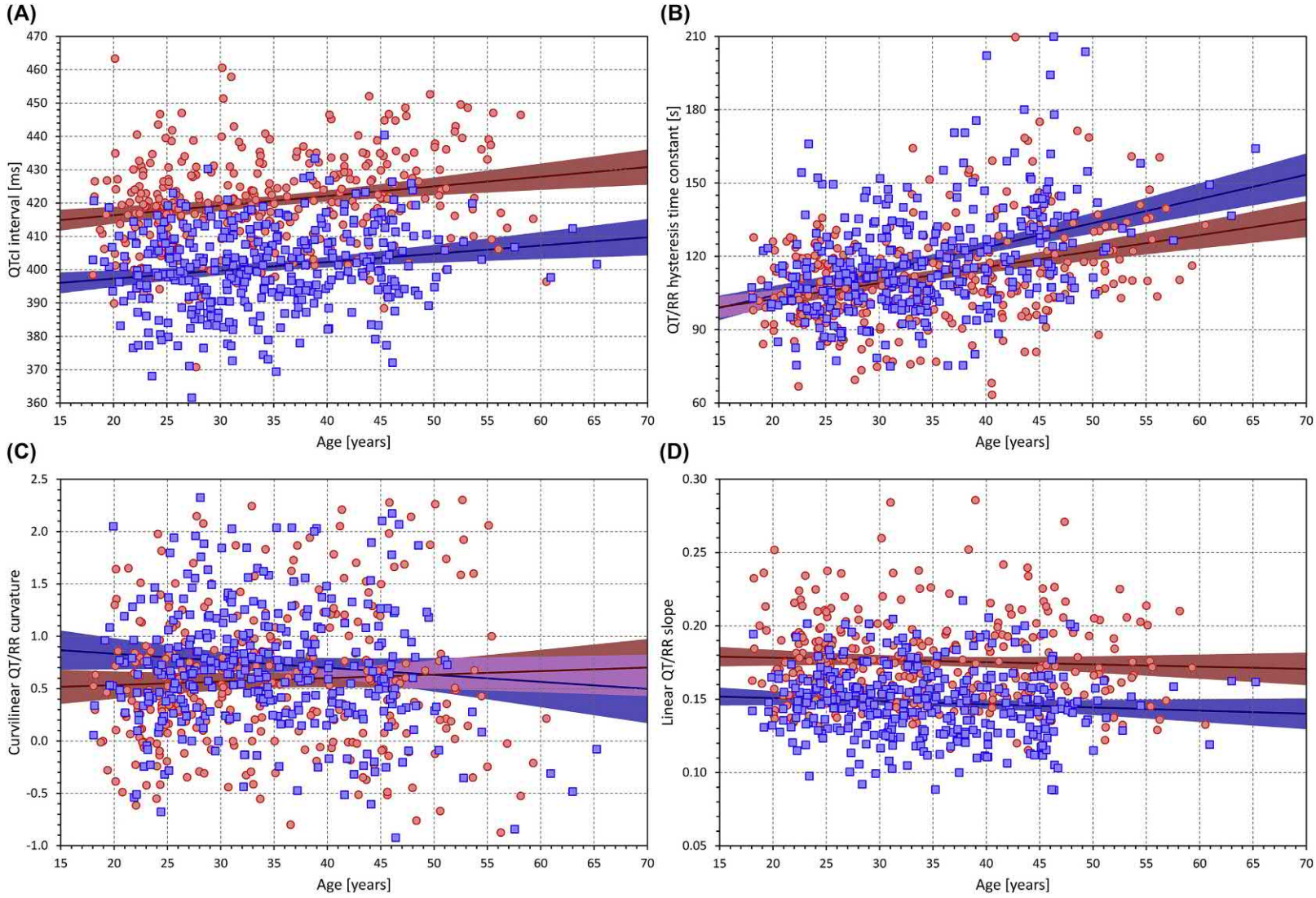

FIGURE 9.14 Scatter diagrams of the ages of the subjects against the *QTc* intervals (subject-specific curvilinear heart rate correction combined with subject-specific hysteresis corrections, *QT*cI) in panel A, subject-specific hysteresis time constant in panel B, curvature coefficient of the subject-specific curvilinear *QT*/*RR*′ regression model in panel C, and the slope of the subject-specific linear *QT*/*RR*′ regression. In all panels, the *red/pink circles* correspond to female subjects and the *blue/light-blue squares* to male subjects. In each panel, the *solid red and solid blue lines* show the linear regressions between the interval durations and ages in females and males, respectively. The red shaded and blue shaded areas are the 95% confidence intervals of the regression lines; the violet areas are the overlaps between the confidence intervals of the sex-specific age-regressions.

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Chapter 10

QT variability and QRST integral

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Introduction

Widely used routine clinical 12-lead surface electrocardiogram (ECG) is based on the assumption that cardiac activation is approximated by a single dipole (heart vector), moving during the cardiac cycle. If there are several simultaneous wavefronts, resultant dipole represents their sum. Therefore, surface ECG characterizes global electrophysiological properties of the heart or global electrophysiological substrate. The global electrophysiological substrate can be more or less homogeneous, and electrical heterogeneity can manifest in space and time. Over the years, several methods were developed to quantify temporal and spatial electrical heterogeneity. In this chapter, we review a few of them: QT variability and QRST integral. While a substantial body of knowledge has been accumulated about underlying mechanisms and clinical utility of each method, very little is known about sex differences in QT variability and QRST integral, mechanisms behind sex differences, and clinical implications of sex differences in QT variability and QRST integral. This review summarizes known findings and highlights knowledge gaps.

Sex differences in QT variability

A comprehensive review of mechanisms, measurements, and clinical usefulness of QT variability was recently published by Baumert et al. [1]. As QT variability was initially developed for risk stratification of sudden cardiac death [2], most of QT variability studies were conducted in heart failure patient populations. Women have a lower prevalence of structural heart disease and are underrepresented in clinical studies of heart failure. In result, in spite of more than 30 years of QT variability research, data of sex differences in QT variability remain scarce.

Studies of healthy middle-aged individuals [3,4] showed that unadjusted QT variability is higher in women than in men. Moreover, unadjusted repolarization lability measured by other metrics (normalized beat-to-beat variability of spatial T axis angle, T loop area, Tpeak−Tend area, and spatial TT angle [5]) is also higher in women than in men [4]. However, women also have other differences with men: smaller T wave amplitude, which is known to be inversely related with QT variability [1,4], longer QT interval (directly correlates with QT variability), and smaller body and heart. In regression analysis, after adjustment for corrected QT interval (QTc), body surface area, and spatial T vector amplitude, there were no differences in QT variability index (QTVI) between men and women [4]. Figs. 10.1−10.3 illustrate sex differences in correlations of QTVI with spatial T vector magnitude, QTc interval, and body surface area (unpublished figures from the study by Sur et al. [4]). Nevertheless, spatial TT′ angle was independently associated with sex, even after adjustment for body surface area, T vector magnitude, and QTc [4]. This finding suggests that different metrics of repolarization lability may reflect different underlying substrate (sex-specific or sex-independent).

Several studies of repolarization lability in a general population were performed. Waks et al. [6] measured spatial TT′ angle in 14,024 participants of the Atherosclerosis Risk in Community (ARIC) study and showed that TT′ angle was significantly larger in women than in men. However, TT′ angle was not corrected for T wave amplitude, which had a strong inverse correlation with TT′ angle. Recently, important study of QT variability in the community was performed by Schmidt et al. [7], who analyzed the data of 2263 participants enrolled in the Sleep Heart Health Study (SHHS). Similarly to previous studies [3,4,6], Schmidt et al. observed that unadjusted QT variability was significantly larger in women than in men. However, corrected for T wave amplitude metric of QT variability (T wave amplitude-corrected standard deviation of QT intervals) [7] did not have sex differences.

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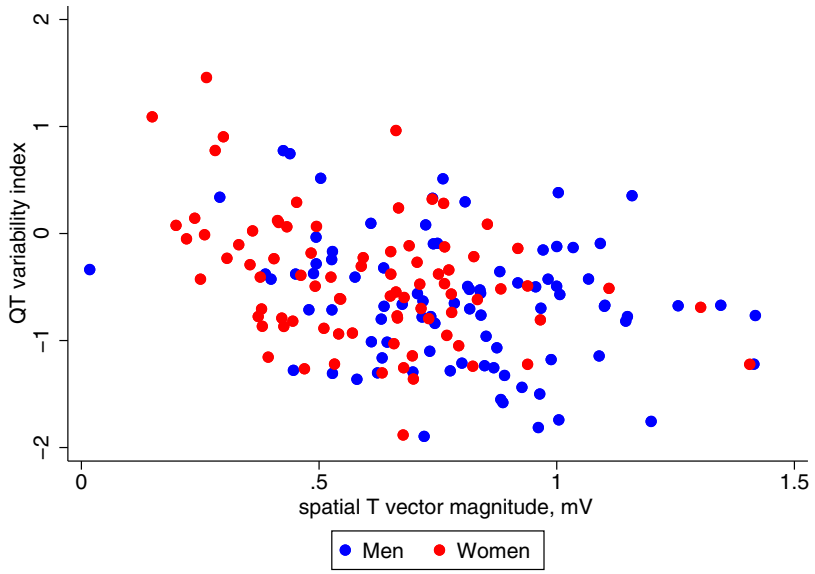

FIGURE 10.1 Scatterplot of mean QT variability index (y-axis) against mean spatial T vector magnitude (x-axis) in men (*blue circles*) and women (*red circles*). *Data from Sur S, Han L, Tereshchenko LG. Comparison of sum absolute QRST integral, and temporal variability in depolarization and repolarization, measured by dynamic vectorcardiography approach, in healthy men and women. PloS One. 2013;8(2):e57175.*

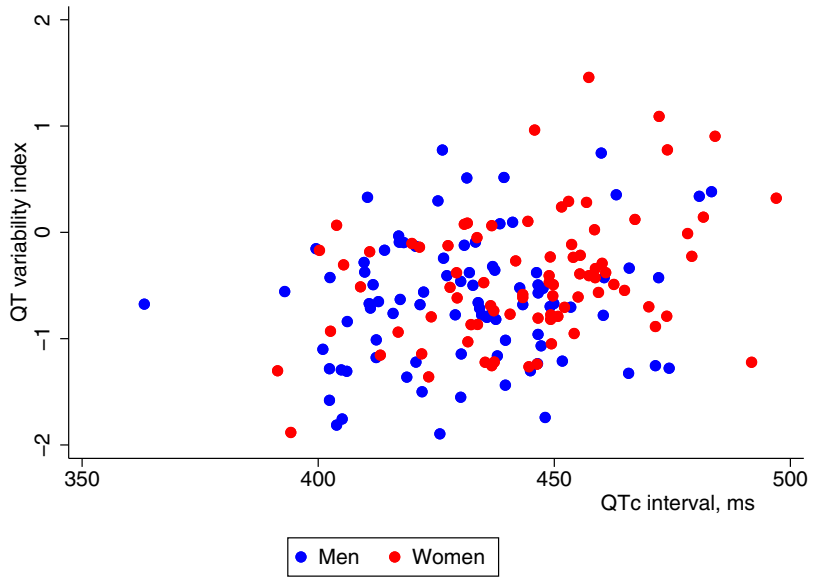

FIGURE 10.2 Scatterplot of mean QT variability index (y-axis) against mean Bazett-corrected QT interval (x-axis) in men (*blue circles*) and women (*red circles*). *Data from Sur S, Han L, Tereshchenko LG. Comparison of sum absolute QRST integral, and temporal variability in depolarization and repolarization, measured by dynamic vectorcardiography approach, in healthy men and women. PloS One. 2013;8(2):e57175.*

Summary of sex differences in QT variability

Sex differences in QT variability do exist. In healthy middle-aged adults, and a general biracial (black and white) population of adults in age 40 years and above, QT variability in women is higher than in men. However, sex differences in QT variability are fully explained by differences in T wave amplitude and differences in body size. Use of T wave amplitude-corrected QT variability measurements is recommended in future studies, to simplify the implementation of QT variability in clinical practice. For repolarization lability measurements that are not corrected for T wave amplitude, sex-specific thresholds have to be developed for future clinical use. Spatial TT′ angle, but not QT variability, may reflect sex-specific substrate in repolarization lability. More studies of sex differences in repolarization lability are needed, to address the significant knowledge gap in understanding mechanisms and clinical implications of sex differences in

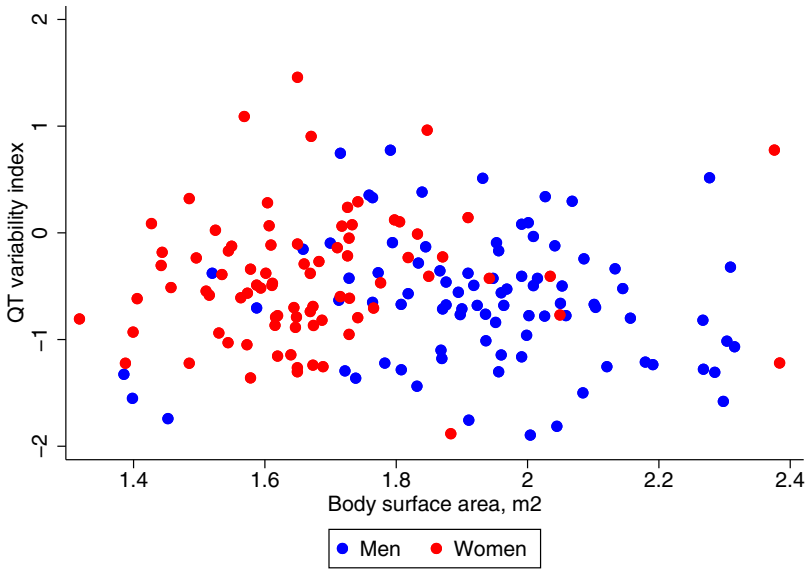

FIGURE 10.3 Scatterplot of mean QT variability index (y-axis) against mean body surface area (x-axis) in men (blue circles) and women (red circles). *Data from Sur S, Han L, Tereshchenko LG. Comparison of sum absolute QRST integral, and temporal variability in depolarization and repolarization, measured by dynamic vectorcardiography approach, in healthy men and women. PloS One. 2013;8(2):e57175.*

repolarization lability in different age and race subgroups. The impact of menopause on QT variability was suggested [8], but was not thoroughly investigated.

Does sex modify the association of QT variability with sudden cardiac death?

Another important question is whether sex modifies the association of QT variability with clinically important outcomes. There were no studies to address this question directly. Only two studies provided relevant data. In the MADIT II study, increased QTVI was associated with sustained ventricular tachyarrhythmia in men but not in women, whereas low coherence between QT variability and heart rate variability was associated with arrhythmic events in women but not in men [9]. In a large prospective cohort ARIC study, Waks et al. [6] reported a trend toward a stronger association of TT′ angle with sudden cardiac death in women than in men, as illustrated in Fig. 10.4. Future studies answering a question of whether sex is an effect modifier in the association of QT variability with clinically important outcomes (sudden death and ventricular arrhythmias) are needed. Evidence of effect modification by sex is a strong argument toward the development of sex-specific risk stratification of sudden cardiac death [10,11].

Sex differences in QRST integral

Sum absolute QRST integral (SAI QRST) [12,13] reflects a scalar measure of Wilson's ventricular gradient [14]. Ventricular gradient defines a vector along which nonuniformity in excitation and repolarization is the most prominent [15,16]. The spatial ventricular gradient (SVG) vector is theoretically independent of the initial site of stimulation, and the SVG points toward the area of the myocardium with the shortest duration of the excited state [17,18]. Independence of the SVG from myocardial activation sequence was reaffirmed in experimental [19] and theoretical studies [20], including studies analyzing human body surface potential mapping [21]. SVG depends on the heterogeneity of action potential area, shape, and duration in the whole heart [22]. Thus, SVG characterizes the magnitude and direction of the steepest gradient between the areas of the heart with the longest and the shortest total recovery time [15,17,23]. In other words, in case if conduction block is present, SVG defines a vector that is perpendicular to the line of conduction block [24]. SVG vector quantifies the global electrical heterogeneity (GEH) of the heart [17]. For a comprehensive assessment of all the properties of GEH, it is necessary to measure five features [25] of the SVG vector on orthogonal XYZ ECG: SVG magnitude, direction (azimuth and elevation), its scalar value (SAI QRST), and spatial QRS-T angle. Spatial QRS-T angle is reviewed in another chapter of this book. In this chapter, we are focusing on sex differences in SAI QRST, SVG magnitude, and direction. A representative example of a vectorcardiogram in healthy men and women is shown in Fig. 10.5.

Very few studies investigated sex differences in SAI QRST. In healthy middle-aged adults, SAI QRST was significantly larger in men than in women [4]. Moreover, after adjustment for body mass index, systolic blood pressure, and QTc, both SVG magnitude and SAI QRST were independently associated with sex. Of note, larger SAI QRST but smaller SVG magnitude was associated

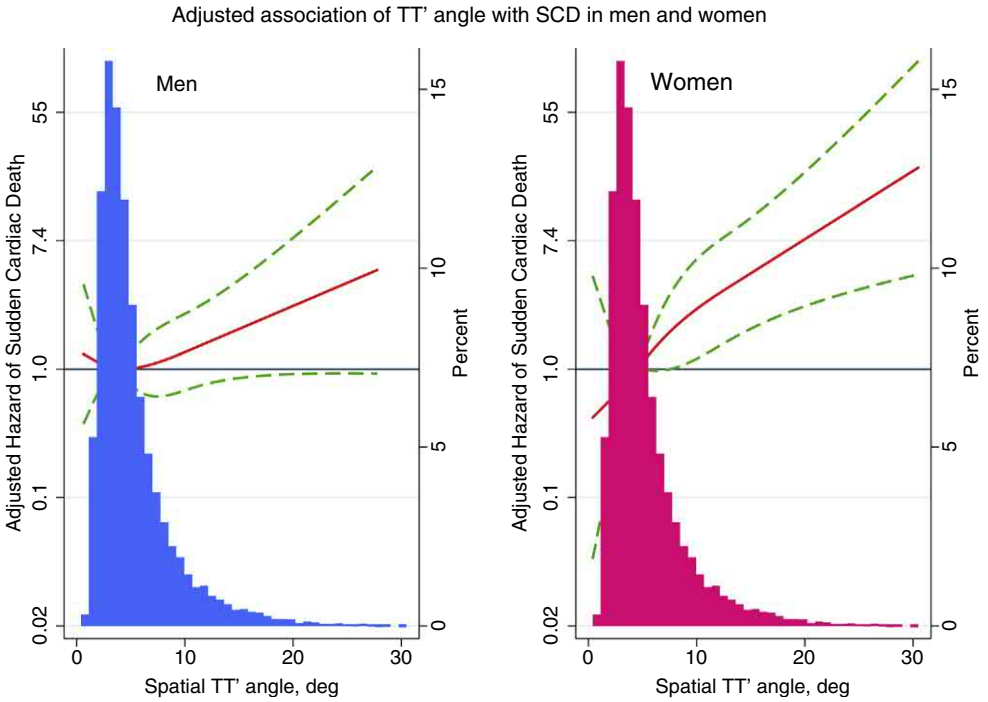

FIGURE 10.4 Multivariate-adjusted hazard ratio (*red line*) with 95% confidence interval (*green dashed lines*) for sudden cardiac death associated with mean spatial TT′ angle (angle between consecutive T vectors) in male and female participants of the Atherosclerosis Risk In Community (ARIC) study. *Modified from Waks JW, Soliman EZ, Henrikson CA, Sotoodehnia N, Han L, Agarwal SK, et al. Beat-to-beat spatiotemporal variability in the T vector is associated with sudden cardiac death in participants without left ventricular hypertrophy: the Atherosclerosis Risk in Communities (ARIC) Study. J Am Heart Assoc. 2015;4(1):e001357.*

with the male sex [4]. In a population of young, healthy athletes, SAI QRST was significantly larger in male (by 52 mV × ms; age-adjusted 95% confidence interval (CI) 36−68 mV × ms) than female athletes, whereas SVG magnitude in male and female athletes did not differ [26]. Two large prospective cohort studies examined SAI QRST in a community. The Finnish Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) showed that SAI QRST was significantly larger in men than in women [27]. In adults of 45−65 years of age, age- and race-adjusted SAI QRST was smaller in women than in men, by 32 mV × ms (95% CI 31−34 mV × ms).

Sex differences in SVG direction seem to be age dependent. In male (but not female) athletes, SVG vector rotated forward with age [26], as illustrated in Fig. 10.6. Nevertheless, in age- and race-adjusted analysis in adults, there was no difference in SVG azimuth between men and women [25]. SVG elevation demonstrated different behavior. In young athletes, there were no sex differences in SVG elevation [26]. However, SVG vector is directed significantly more upward in adult men as compared to adult women [25].

Summary of sex differences in QRST integral

In summary, there are significant sex differences in SAI QRST. SAI QRST is significantly greater in men than in women. The degree of difference in SAI QRST between men and women is age dependent. Moreover, there are significant age-dependent differences in SVG direction between men and women. Further studies of SAI QRST in male and female individuals of various age categories are needed, to understand their mechanisms and clinical implications. Available data suggest that SAI QRST and SVG may represent sex-specific electrophysiological substrate. Sex-specific thresholds for SAI QRST have to be validated in different populations for its implementation in clinical practice. Further studies of sex differences in SVG direction and magnitude are needed.

Does sex modify the association of QRST integral with clinical outcomes?

Very few previous studies addressed this important question. Lipponen et al. reported that in KIHD study, SAI QRST was a strong and independent predictor of cardiovascular mortality in the female population, but not in males [27]. Consistently with KIHD study results, in ARIC study SAI QRST was significantly stronger associated with sudden cardiac death in women (adjusted Cox regression Hazard Ratio (HR) 1.25 (95% 1.08−1.45) than in men (HR 1.13 (95% CI 1.03−1.24); P for interaction 0.024. Importantly, while KIHD and ARIC cohorts analyzed different

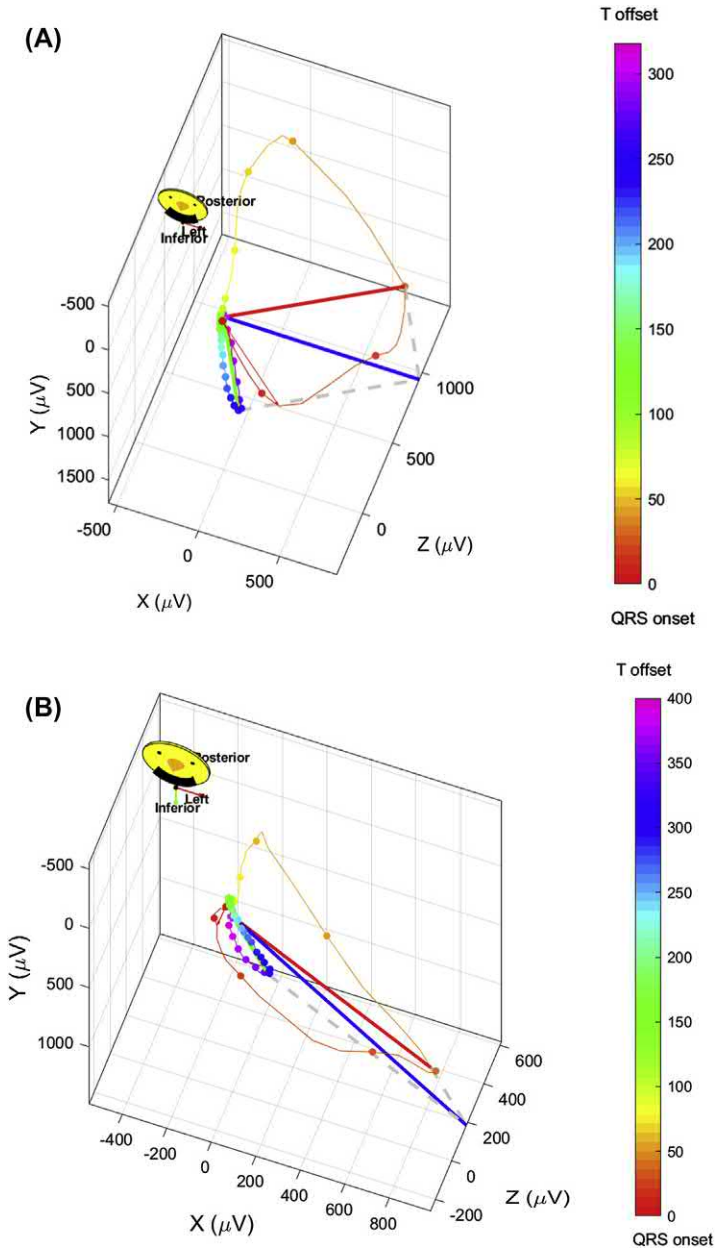

FIGURE 10.5 A representative example of vectorcardiogram in healthy men (A) and women (B). Spatial peak vectors are shown.

ECG signal, both studies obtained nearly identical threshold for abnormal SAI QRST. KIHD cohort analyzed recorded Frank orthogonal XYZ ECG signal and used 90th percentile to define abnormal SAI QRST, defined as above 180 mV × ms in white women. ARIC cohort recorded 12-lead ECG and then transformed it into orthogonal XYZ signal. Youden index was used to identify the best threshold for abnormal SAI QRST, which was above 178 mV × ms for white women. Such consistency confirms the robustness of SAI QRST measurements. Further studies are needed to definitively answer a question of whether sex modifies the association of QRST integral with clinical outcomes.

Genomics of QRST integral

Genome-wide association study (GWAS) of GEH in approximately 14,000 participants of ARIC and Cardiovascular Health Study (CHS) identified ten genetic loci, associated with GEH [28]. While specific biological function behind detected genetic "tags" is unknown and requires further study, these first GEH GWAS findings shed light on underlying mechanisms of GEH.

Four out of ten loci are novel and have not been previously reported associated with any other ECG phenotype: loci on chromosomes 9 (near *HMCN2*), 15 (*IGF1R*), 11 (11p11.2 region cluster), and 7 (near *ACTB*).

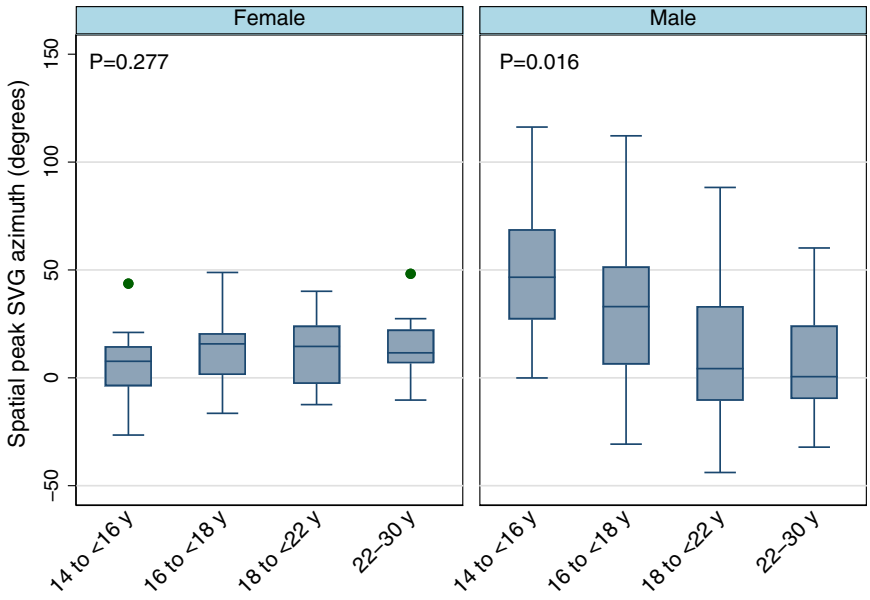

FIGURE 10.6 Boxplot of peak spatial ventricular gradient (SVG) azimuth in male and female athletes of four age categories (14 to <16 years, 16 to <18 years, 18 to <22 years, and 22−30 years). Median (*dark horizontal line* crossing the box) and interquartile range (IQR) (box) are plotted. Whiskers specify the adjacent values, defined as the most extreme values within 1.5 IQR of the nearer quartile. *Modified from Thomas JA, E AP-A, Junell A, Newton K, Hamilton C, Li-Pershing Y, et al. Vectorcardiogram in athletes: the sun valley ski study. Ann Noninvasive Electrocardiol. 2019;24(3):e12614.*

Three out of ten loci are in proximity to previously reported variants, but not in linkage disequilibrium with them, thus representing independent signals: lncRNA (*RP11-481J2.2*), a locus on chromosome 1 (*LUZP1-KDM1A*), and on chromosome 3 (*SCN5A*), which is located on a well-known sodium channel gene. Three GEH-associated loci (near *TBX3*, *HAND1*, and *NFIA*) are known loci, associated with QRS duration and PR interval. Most (7/10) loci remained associated with GEH phenotypes after additional adjustment for traditional ECG metrics.

The strongest GEH-associated locus was mapped near the *TBX3* gene, which plays a crucial role in the development of the cardiac conduction system. *TBX3* determines the fate of cardiac progenitor cells regarding whether or not it becomes a cell with central conduction system properties (i.e., with the function of automaticity), or myocardial cell. *TBX3* deficiency can also lead to the insufficient development of the atrioventricular node, which might manifest as prolonged PR.

It will be necessary to validate the results of the first genomic study of QRST integral. After validation, results of GWAS will help to uncover underlying biology behind GEH, which in the future can lead to the development of novel therapies.

Summary

In summary, the striking paucity of the data regarding sex differences in QT variability and QRST integral calls for future studies to address this knowledge gap. Studies of sex differences in all age groups are needed, as available data suggest that sex differences are age dependent. Studies of sex differences in different populations across the continuum of cardiovascular disease are needed. Development of sex-specific thresholds of ECG markers is required for improved accuracy of risk stratification and clinical interpretation of ECG findings. Special attention should be paid to answering a question about effect modification by sex. Presence of significant effect modification requires the development of sex-specific risk prediction models, whereas an absence of effect modification does not. A better understanding of mechanisms and clinical implications of sex differences in QT variability and QRST integral will lead to an improvement in clinical outcomes in both sexes, in men and women.

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Chapter 11

T-wave morphology indices

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The usefulness of QT interval duration and of its rate corrected duration for the assessment and monitoring ventricular repolarization was established shortly after the inventions of electrocardiography. Indeed, QT interval measurement still belongs to the essential components of electrocardiogram (ECG) evaluation.

Nevertheless, it is also understood that QT interval duration alone does not fully characterize the ECG patterns of repolarization. Abnormalities in the shape of the T wave may also be observed during ECG diagnostics. These can be present in combination with both normal and abnormal QT interval duration. Occasionally, the terminology of "nonspecific T-wave changes" is used, but this vague expression only hides the fact that no insight into the causes or mechanisms of repolarization abnormalities is provided.

Number of attempts have been made to advance the ECG-based repolarization assessment beyond the QT interval duration. Some two or three decades ago, the concept of the so-called QT interval dispersion (that is the difference in QT interval durations among different ECG leads) was proposed [1] and gained some popularity before it was recognized that this "dispersion" is only caused by a combination of measurement artifacts with spatial vectorcardiographic projections [2–4]. It is therefore not surprising that the expected usefulness of QT dispersion failed to materialize [5–7]. It remains to be seen whether other simple interval-based characteristics of T-wave shape, e.g., the more recently proposed measurement of the interval between the peak and the end of the T wave [8], will overcome the problems of QT dispersion. Indeed, some consider these new proposals equally questionable [9].

Advances of digital ECG acquisition enabled more advanced methodologies for the quantification of T-wave morphology. Among others, it became possible to extend the characterization of T-wave shapes beyond singular ECG leads by combining different ECG leads in multidimensional algebraic computations [10]. A seminal system offering a battery of multilead morphological indices for T-wave description in standard 12-lead ECGs was developed by Acar et al. [11]. The system by Acar et al. and its subsequent extensions [12] included several indices that proved to be a considerable value in risk stratification and other clinical research studies.

Of these indices, the most frequently used is the spatial angle between the QRS and T-wave vector orientations (angle of the so-called ventricular gradient initially proposed by Wilson [13]). Since the seminal observation that an increased spatial QRS-T angle is a risk predictor among postinfarction patients [14], the power of this risk predictor has been repeatedly confirmed in a number of investigations researching both cardiac patients and general populations [14–20]. The value of spatial QRS-T angle has also been repeatedly reviewed [21].

Sex differences of the QRS-T angle are also known. Initially, these were studied by Smetana et al. [22] who used the implementation from the system by Acar et al. Consistent with subsequent studies, Smetana et al. confirmed that the angle is smaller in females compared to males. Sex-specific normality limits of the QRS-T angle have been derived in the large ARIC study that found the upper normality limits being some 20 degrees smaller in females compared to males [23].

Another risk factor derived from the system by Acar et al. is based on the measurement of the extent of the ECG signal from multiple leads that can be explained by vectorcardiographic dipole movement. That is, algebraic concept of singular value decomposition [24] is used to extract the spatial orientation (usually denoted as S1 direction) that contains most of the voltage movement within the QRS-T complex. Once this portion of the signal is removed from the original ECG, the process is repeated, and again, the orientation of S2 containing the largest part of the remaining signal is found. This S2 orientation must be perpendicular to the initial dominant direction S1 because, otherwise, part of the remaining signal could still be projected into the S1 direction thus to belong to the part

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of the signal that was removed in the first step. Repeating this process again creates the S3 direction that contains most of the signal that cannot be explained by vector movement within the S1 and S2 plane. The combination of the signals in the S1, S2, and S3 directions creates a three-dimensional vector movement that corresponds to the vectorcardiographic loop. This creates the perpendicular system of directions S1, S2, and S3, which are rotated from the standard XYZ perpendicular axes to obtain the maximal signal components in these new directions. (That is, the standard perpendicular coordinates XYZ might be rotated so that the vectorcardiographic loop in the XYZ coordinates coincides with the loop in the S1, S2, and S3 coordinates.)

Nevertheless, even in physiologic normal 12-lead ECG signals, the combination of signals in the S1, S2, and S3 directions (which is the same as multilead ECG reconstruction from orthogonal XYZ vectorcardiograms) does not explain all the multilead compositions of individual leads. Since the standard 12-lead ECG contains eight algebraically independent leads I, II, V1, …, V6 (leads III, aVR, aVL, and aVF are simple combinations of signals recorded in leads I and II), the process of decomposing the signal into further directions can be repeated 8 times creating directions S4, S5, …, S8 (in multilead body surface maps, the process can continue into further components). While these additional directions S4, …, S8 are beyond three-dimensional spatial understanding (thus representing algebraic rather than spatial dimensions [12]), it is easy to understand that the signal represented by these additional components cannot originate from processes synchronized across the complete ventricular myocardial mass, simply because signals that do originate from synchronized processes are embedded into the S1, S2, and S3 system. Therefore, the extent of the signals in the S4, …, S8 directions represents a derived measurement of localized heterogeneities contributing to the 12-lead ECG signal.

Numerical expression of the signals in the S4, …, S8 directions belonging to the T wave has been termed the "T-wave residua" (TWR) [12] and expressed either as the absolute magnitude of the signal in the S4 to S8 directions or as a relative number of the proportion between the magnitudes of the S4 to S8 signals and the S1 to S3 signals. Both variants of the TWR have been also found to predict arrhythmic and other cardiovascular risk in both cardiac patients and in other clinically well-defined populations [25–28]. Physiologic studies of autonomic provocations also showed that the TWR are under the influence of the autonomic nervous system [29]. This suggests that the assessment of TWR may offer direct estimation of the autonomic influence on ventricular repolarization, which would explain a possible mechanistic link to the powerful risk prediction. Sex differences have also been reported for TWR in healthy population suggesting increased values in healthy females compared to males [22].

Many other T-wave morphological indices have been proposed including further components in the system developed by Acar et al. [11]. As an example, the so-called T-wave morphology dispersion (TMD) considers directions of vectors defined by the projection of the spatial vectorcardiographic T-wave loop into individual leads of the standard 12-lead ECG. In physiologic normal recordings with a narrow and smoothly shaped T-wave loop, these directions are less different from lead to lead compared to abnormal recordings with distorted T-wave shapes. This is reflected in the TMD method that is based on the spread of the orientations of the individual lead projections.

Many of the T-wave morphological indices have been found to be influenced by the underlying heart rate [30], but systematic studies of their heart rate dependency are presently still lacking. Only a relatively simple study [31] showed that some of these indices adapt to the abruptly changing heart rate much faster than the duration of the QT interval, which exhibits substantial hysteresis delay [32,33]. This chapter therefore shows the sex differences in the three mentioned T-wave morphology indices including the sex differences in their heart rate dependency.

T-wave morphological indices

Spatial QRS-T angle

There are different methods to calculate the QRS-T angle from digital ECG signals [21]. Recently, it was shown that these methods do differ not only in their algorithmic implementation but also in the reproducibility and clinical applicability [34]. Three principally different approaches may be distinguished, each combined with different possibilities of obtaining the representation of the multilead ECG signals in three orthogonal leads. An orthogonal representation of a 12-lead ECG recordings can either be obtained using a suitable transformation matrix that recalculates the voltages in XYZ leads from the voltages of the algebraically independent leads of a standard 12-lead system [35–37] or be generated by the singular value decomposition as just described, i.e., obtaining the voltages in the orthogonal S1, S2, and S3 leads [11,38]. Either of these processes leads to a matrix of orthogonal leads $x(t)$, $y(t)$, and $z(t)$ where the time variable t spans from the beginning of the QRS complex to the end of the T wave.

The simplest expression of the QRS-T angle is based on the maximum vector magnitudes of the QRS complex and T-wave vectrocardiographic loops. That is, a vector magnitude signal $V(t) = \left(x^2(t) + y^2(t) + z^2(t)\right)^{1/2}$ is constructed and time instances μ_{QRS} and μ_{T} are found when the vector magnitude signal is largest within the QRS complex and within the T wave, i.e., $V\left(\mu_{\mathrm{QRS}}\right) = \max_{t\in \mathrm{QRS}} V(t)$ and similarly $V(\mu_{\mathrm{T}}) = \max_{t\in \mathrm{T}} V(t)$.

The QRS-T angle is subsequently calculated between the three-dimensional vectors $[x(\mu_{QRS}), y(\mu_{QRS}), z(\mu_{QRS})]$ and $[x(\mu_T), y(\mu_T), z(\mu_T)]$. This approach is based on the assumption that the vectors at which the vector magnitude signal is the largest reasonably represent the spatial orientation of the QRS and T-wave loops. Nevertheless, this assumption is rather simplistic since even in normal physiologic ECGs, the QRS complex loop (and occasionally also the T-wave loop) has a complex morphology that cannot be represented by a single direction (Fig. 11.1).

A somewhat more realistic approach is thus to calculate and average all vectors $[x(t), y(t), z(t)]$ weighted by their magnitude for the time variable t passing through the QRS complex and through the T wave and to calculate the spatial angle between the vectors given by these vectorial weighted averages. Mathematically, this corresponds to the calculation of the angle between vectors $\left[\int_{t\in QRS} x(t)dt, \int_{t\in QRS} y(t)dt, \int_{t\in QRS} z(t)dt\right]$ and $\left[\int_{t\in T} x(t)dt, \int_{t\in T} y(t)dt, \int_{t\in T} z(t)dt\right]$, where $t\in$ QRS and $t\in$ T means that the time index t ranges from the onset to the offset of the QRS complex and the T wave, respectively. This means that the angle is calculated between the vectors given by the areas under each of the orthogonal leads within the QRS complex and within the T wave.

While this approach is intuitively more accurate compared to the approach based on the simple maximum of vector magnitude, it still assigns a singular direction to both the QRS complex and the T-wave loops. To avoid this, a combination of the shapes of the loops is possible by calculating the angles between all possible combinations of the QRS and T-wave vectors and obtaining a weighted average of such angles using the weights given by products of the vector magnitude of the vectors. Formally, this corresponds to the calculation $\frac{\left(\int_{t\in QRS}\int_{u\in T}(\Phi([x(t),y(t),z(t)],[x(u),y(u),z(u)])*V(t)*V(u))dudt\right)}{\left(\int_{t\in QRS}\int_{u\in T}(V(t)*V(u))dudt\right)}$ where $\Phi(\mathbf{M},\mathbf{N})$ is the angle between two vectors $\mathbf{M},\mathbf{N}$.

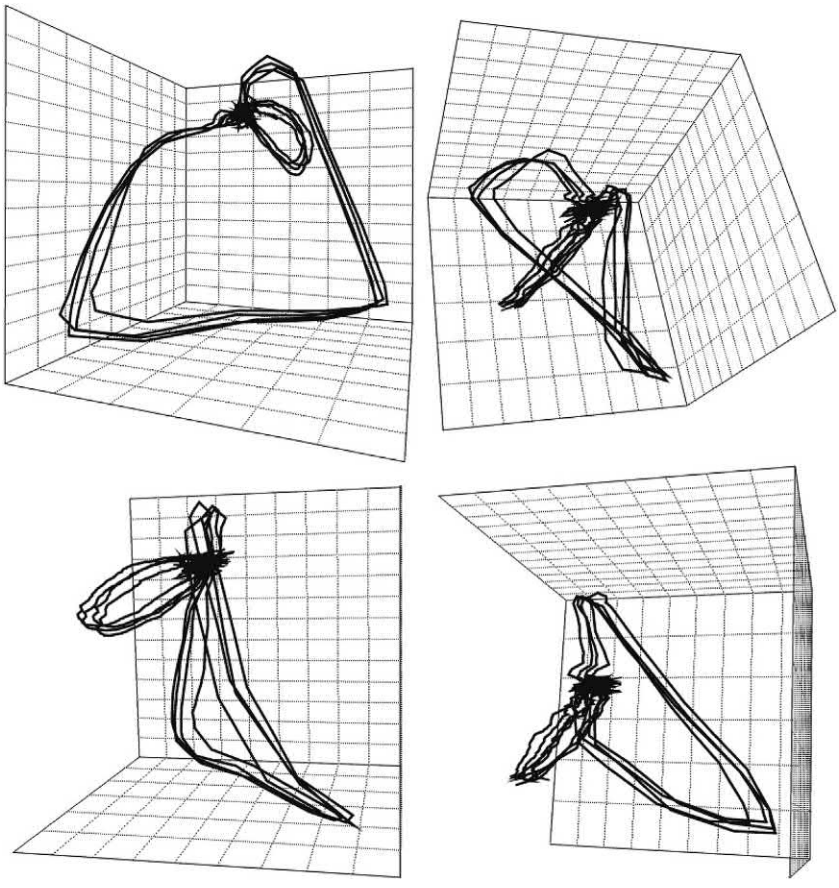

FIGURE 11.1 The individual panels of the figure show four different projections of the three-dimensional representation of the same short-term electrocardiogram of a normal healthy subject. (The images show superimpositions of the vectorcardiographic loops of the same four cardiac cycles.) The images of the different panels only differ in the point of view on the spatial structure of the vectorcardiographic loops. Note that while the spatial orientation of the T-wave loop (the small narrow coil) is easy to define, the QRS complex loop (the large broad loop) in the system of the three orthogonal coordinates is twisted into a convoluted shape that cannot be represented by a singular spatial orientation.

T-wave morphology dispersion

As already described, the TMD index is based on the spread of orientation along which the three-dimensional T-wave loop projects into individual ECG leads. If the vector Θ_L represents the three-dimensional direction along which the T-wave loop projects into an ECG lead (for L = I, II, V1, V2, …, V6), the spread of the vectors can be calculated as the average of angles between different pairs of these vectors. The calculation of TMD also reflects the fact that lead V1 is oriented towards the atria rather than the ventricles and therefore is omitted from the construction. Considering all other algebraically independent leads, it is possible to consider 21 different pairs of leads. Therefore, TMD is calculated as $\frac{1}{21}\sum_{l,k}\Phi(\Theta_l,\Theta_k)$, where $l,k\in\{I,II,V_2,V_3,V_4,V_5,V_6\}$ and, as in the previous section, $\Phi(\mathbf{M},\mathbf{N})$ is the angle between vectors $\mathbf{M},\mathbf{N}$.

Nondipolar T-wave components

As previously described [11,12,38], the extraction of the S1, S2, …, S8 leads from the standard 12-lead ECG signal is based on the computation of the so-called eigenvalues σ_1 σ_2, …, σ_8. Where σ_i represents the energy of the T-wave signal in the ith orthogonal lead Si. Because the maximum energy in one direction is always extracted in each of the decomposition steps, the eigenvalues are always monotonically decreasing, i.e., $\sigma_1 \geq \sigma_2 \geq \sigma_3 \geq \ldots \geq \sigma_8$. Since the leads S1, S2, and S3 represent the vectorcardiographic three-dimensional loop (albeit in optimally rotated coordinates), the eigenvalues σ_1, σ_2, and σ_3 represent the power of the T-wave signal attributable to the T-wave loop. The eigenvalues σ_4 σ_5, …, σ_8 represent the power of the ECG signal that cannot be attributed to the three-dimensional loop. Therefore, the relative TWR are defined as $\text{TWR} = \sum_{i=4}^{8}\sigma_i \Big/ \sum_{i=1}^{8}\sigma_i$.

Investigated population

To demonstrate the sex differences of the described T-wave morphological indices, we used data available from a pharmacology investigation conducted in healthy subjects. All subjects had a normal screening ECG and normal clinical assessment usual in clinical pharmacology studies [39]. The study was appropriately ethically approved; all participants gave written informed consent.

The study investigated 176 healthy females (aged 32.7 ± 9.8 years) and 176 healthy males (aged 33.5 ± 8.4 years; no statistical differences between ages of females and males). Female subjects of the study had a negative pregnancy test and for the duration of the clinical pharmacology study were not on hormonal contraceptives or any other hormonal therapy.

Repeated 12-lead daytime Holter recordings were made in all study subjects while they were on no treatment. During these recording days, the subjects did not smoke and were not permitted to consume alcohol or caffeinated drinks. Of these Holter recordings, 10-s ECG segments were extracted from episodes of different heart rates. Each 10-s ECG segment was used to construct a representative beatform of the QRS-T complexes. In these, QRS onset, QRS offset, and T-wave offset were measured using previously described technology [40,41].

After the exclusion of 0.08% of the extracted ECG segments that were too noise polluted to allow reasonable T-wave morphology assessment, the data set provide a total of 480,375 individual measurements. On average, there were 1347 ± 203 and 1383 ± 186 measurements made in individual female and male subjects, respectively. In addition to the described T-wave morphological indices, averaged RR interval duration in each of the 10-s ECG segments was obtained and used to express the underlying heart rate.

Subsequently, the individual T-wave morphology indices were summarized in each subject in different heart rate bins and in different periods of the time of the day. They were also related to the underlying heart rate using simple linear regression models. No time-delay adaptation to the changing heart rate was considered since previous investigations suggested that this omission does not lead to substantial inaccuracies [31].

The residuals of the linear regression models were used to compare the stability of the different methods for the QRS-T angle computations. Fig. 11.2 shows that the lowest intrasubject residuals were obtained with the combined integrative approach suggesting that this method of calculation leads to the most stable measurements (which is consistent with previous comparisons of clinical applicability [34]). Fig. 11.2 presents the comparisons based on the orthogonal conversion based on the singular value decomposition method. The orthogonal conversion based on general conversion matrix [37] led to larger regression residuals and thus provided QRS-T angle measurements that showed lesser intrasubject stability.

Sex differences

Similar to other electrocardiographic indices, T-wave morphology characteristics show substantial intersubject variability combined with a reasonable intrasubject stability. Such intersubject differences exist in both females and males and their examples are shown in Figs. 11.3–11.6.

Rate dependency

In each of the researched subjects, the investigated indices were grouped into heart rate bins, which contained all the

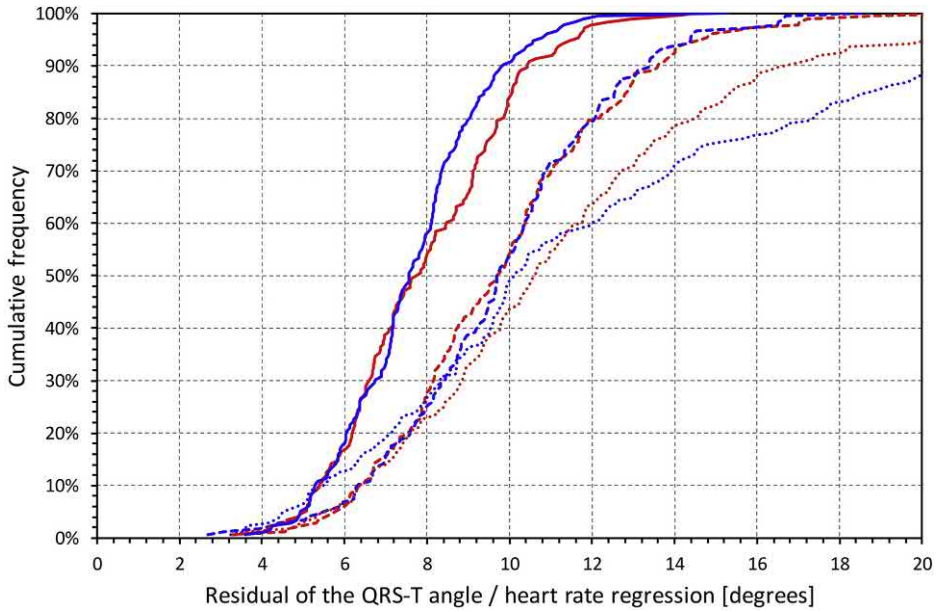

FIGURE 11.2 In the investigated electrocardiograms of healthy subjects (see the text for details), different computation possibilities of deriving the QRS-T angle were applied to the orthogonal representation obtained by singular value decomposition. In each subject, multiple measurements of the QRS-T angle were linearly related to the underlying heart rate and the regression residua (i.e., the spreads of the measured values along the regression lines) were used as indicators of the measurement stability of different methods of QRS-T angle computations. The figure shows cumulative frequency distributions of the residua obtained by the different methods. The *dotted, dashed, and full lines* show the residua of the maximum vector, QRS and T-wave areas, and the combined integral approach, respectively. *Red and blue lines* correspond to the female and male subpopulations, respectively. Note that the residuals of the combined integral method were (statistically significantly) smaller than those achieved by the other methods confirming that this method of the QRS-T angle computation was more accurate.

measurements with heart rate differing from the central value of the bin by less than ±5 beats per minute (bpm). In each heart rate bin, the median value of the index was calculated in each subject. Fig. 11.7 shows the statistical summaries of these median bin values and their comparison between female and male subjects.

As seen in Fig. 11.7, QRS-T angles are increasing with increasing heart rate in both females and males. The extent of the increase is similar in both sexes and the difference of some 10−15 degrees (with females having the angle lower than males) shows only modest increase with the increasing rate. In terms of population values, TMD seems to be almost heart rate independent and shows averaged female values being approximately 2−3 degrees larger compared to the measurements in males.

Substantial sex differences appear to exist in the heart rate responses of T-wave residuum. Fig. 11.7 shows that in males, the TWR values increased from the central value around 0.01% almost linearly to 0.04% when the heart rate was elevated from 60 to 100 bpm. On the contrary, the same heart rate changes in females led to the increase of the TWR central values from approximately 0.03% to approximately 0.09%, but this increase was not linear and showed steeper rate responses at faster compared to slower rates.

The sex differences in the relationship to heart rate observed in Fig. 11.7 were confirmed by the investigations of the slopes of the intrasubject linear regressions relating the T-wave morphological indices to the underlying heart rate (Fig. 11.8). While there were no noticeable sex differences in these slopes for the QRS-T angle, there were some females and males in whom the slope of the TMD/heart rate regression was negative with others in whom this slope was positive. This led to the constant heart rate−independent population levels seen in Fig. 11.7.

The slopes of the TWR/heart rate regressions showed substantial sex differences and were substantially steeper in females compared to males. The rate dependency patterns shown in Fig. 11.7 as well as the individual examples in Figs. 11.3−11.6 also suggest that the simple linear relationships of TWR measurements to the underlying heart rate are too simplistic. More advanced methods are needed to investigate the TWR/heart rate relationship in more detail. Potentially, the same criticism may also apply to the heart rate dependency of the QRS-T angle and TMD values. Nevertheless, the observations summarized in Fig. 11.7 have not been based on any regression models and thus this possible criticism does not apply to the observed sex differences.

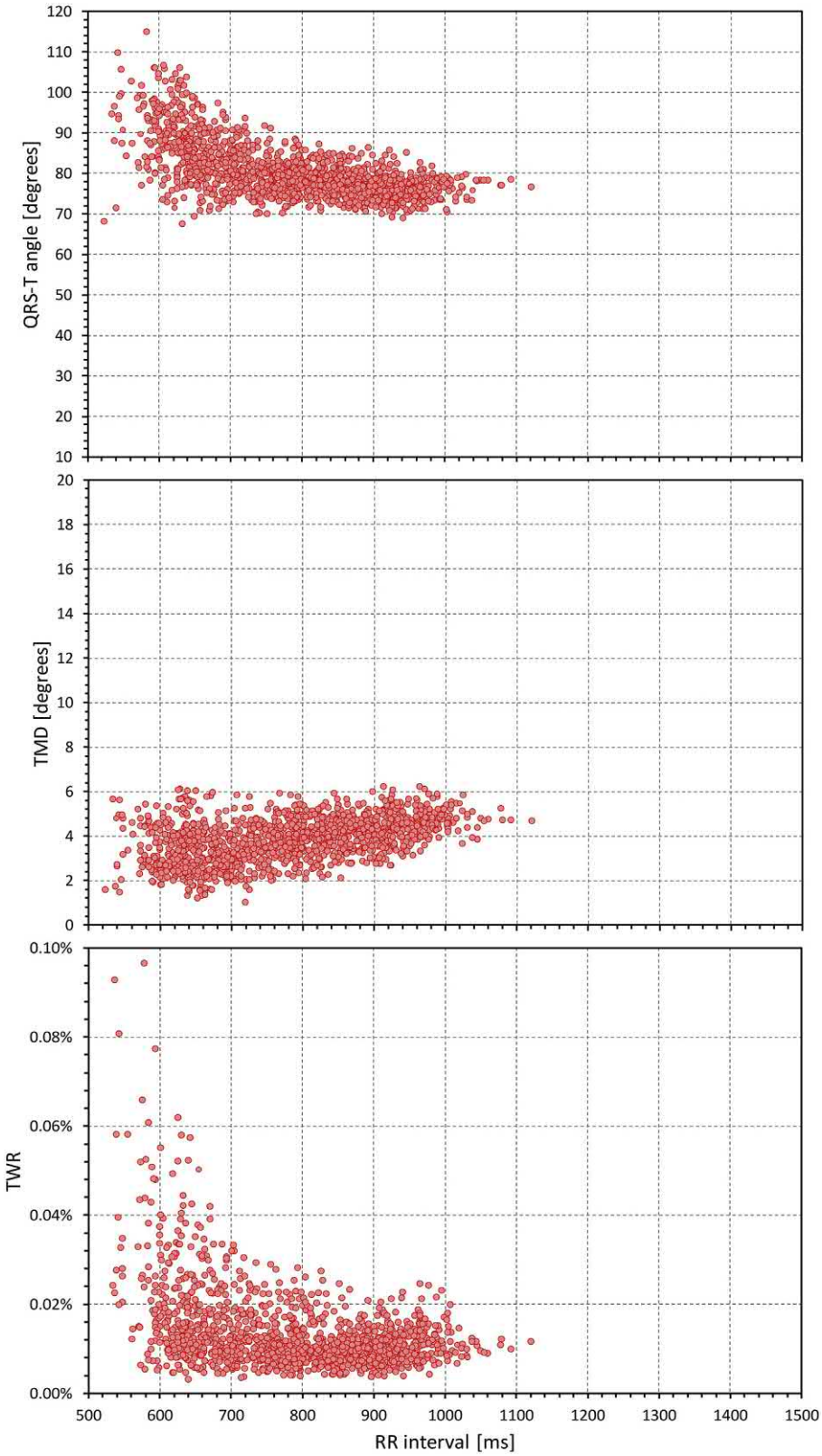

FIGURE 11.3 Scatter diagrams between RR intervals and the spatial QRS-T angle (top panel), T-wave morphology dispersion index (middle panel), and nondipolar T-wave residua (bottom panel) in a healthy 25-year-old female. Compare with Figs. 11.4–11.6 and note that these figures show examples of female and male subjects in whom the comparison of the QRS-T angles is the opposite of that found statistically in the population.

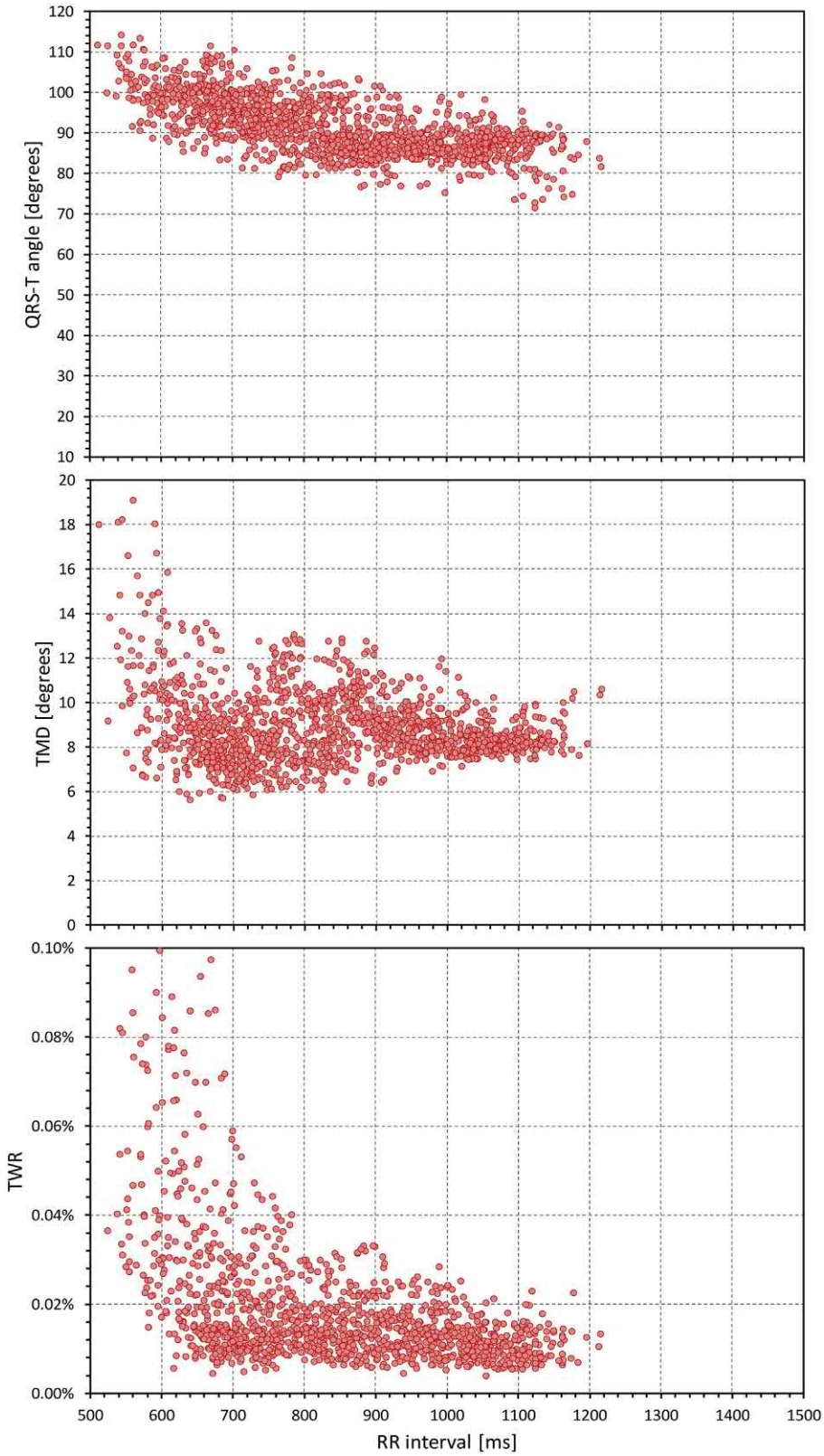

FIGURE 11.4 Scatter diagrams between RR intervals and the spatial QRS-T angle (top panel), T-wave morphology dispersion index (middle panel), and nondipolar T-wave residua (bottom panel) in a healthy 27-year-old female. Compare with Figs. 11.3, 11.5, and 11.6 and note that these figures show examples of female and male subjects in whom the comparison of the QRS-T angles is the opposite of that found statistically in the population.

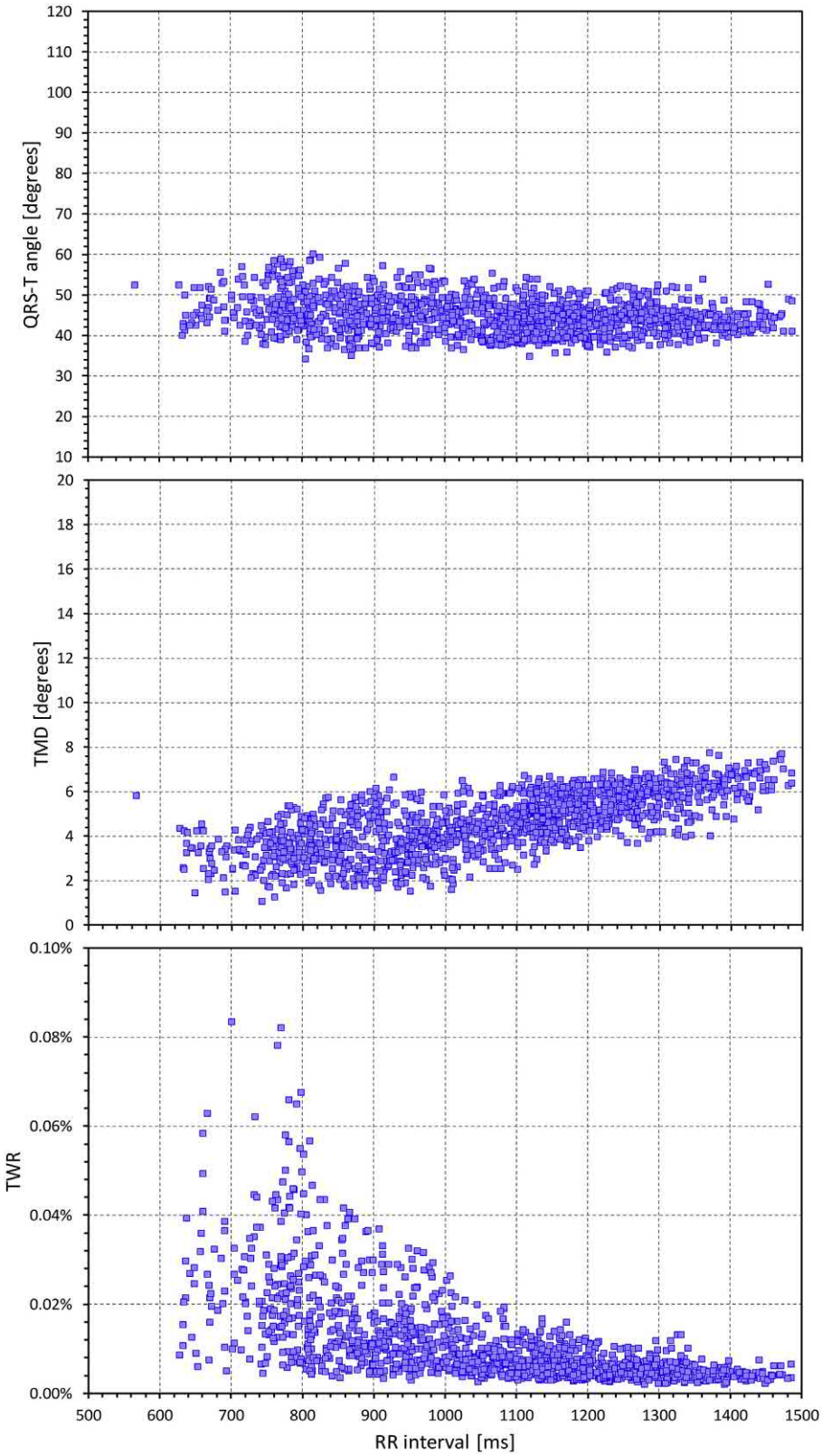

FIGURE 11.5 Scatter diagrams between RR intervals and the spatial QRS-T angle (top panel), T-wave morphology dispersion index (middle panel), and nondipolar T-wave residua (bottom panel) in a healthy 28-year-old male. Compare with Figs. 11.3, 11.4, and 11.6 and note that the figures show examples of female and male subjects in whom the comparison of the QRS-T angles is the opposite of that found statistically in the population.

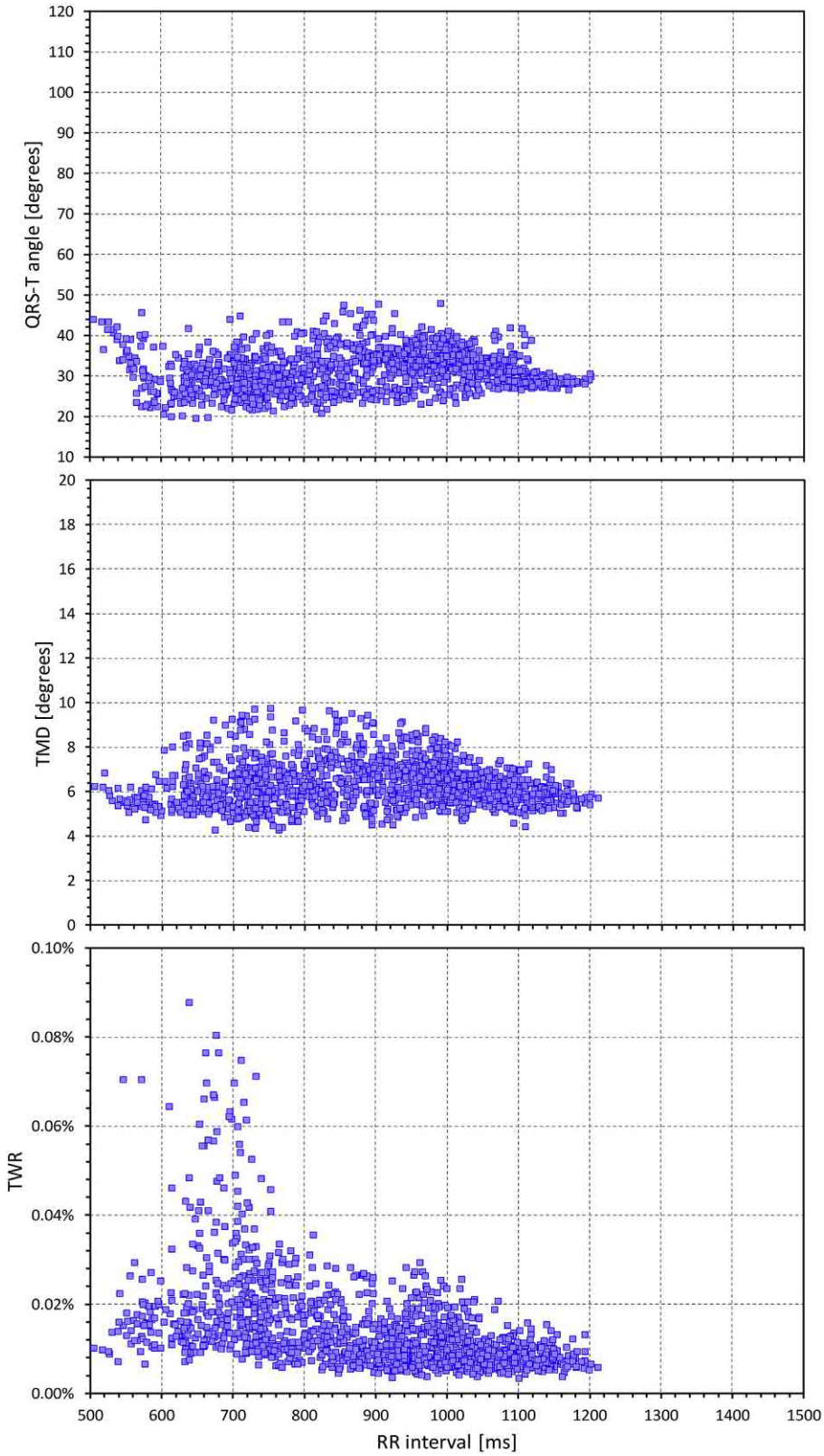

FIGURE 11.6 Scatter diagrams between RR intervals and the spatial QRS-T angle (top panel), T-wave morphology dispersion index (middle panel), and nondipolar T-wave residua (bottom panel) in a healthy 38-year-old male. Compare with Figs. 11.3–11.5 and note that the figures show examples of female and male subjects in whom the comparison of the QRS-T angles is the opposite of that found statistically in the population.

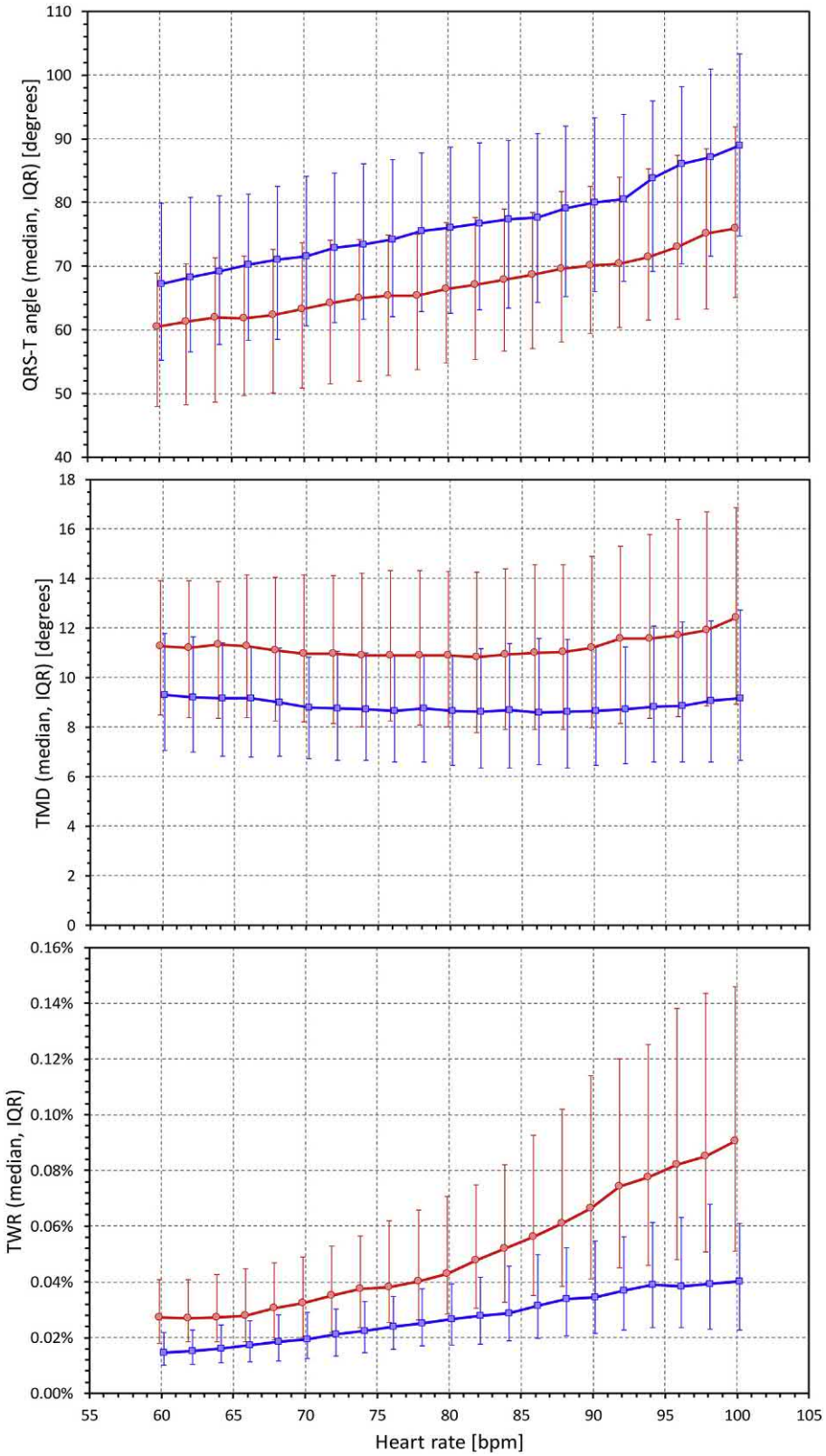

FIGURE 11.7 Heart rate dependency of QRS-T angle (top panel), T-wave morphology dispersion (TMD, middle panel), and relative T-wave residua (TWR, bottom panel) in the investigated population of healthy subjects (see the text for details). In each panel, the *red and blue lines* correspond to female and male subpopulations, respectively. For each heart rate bin, the panels show the median population value; the error bars show the interquartile range (IQR).

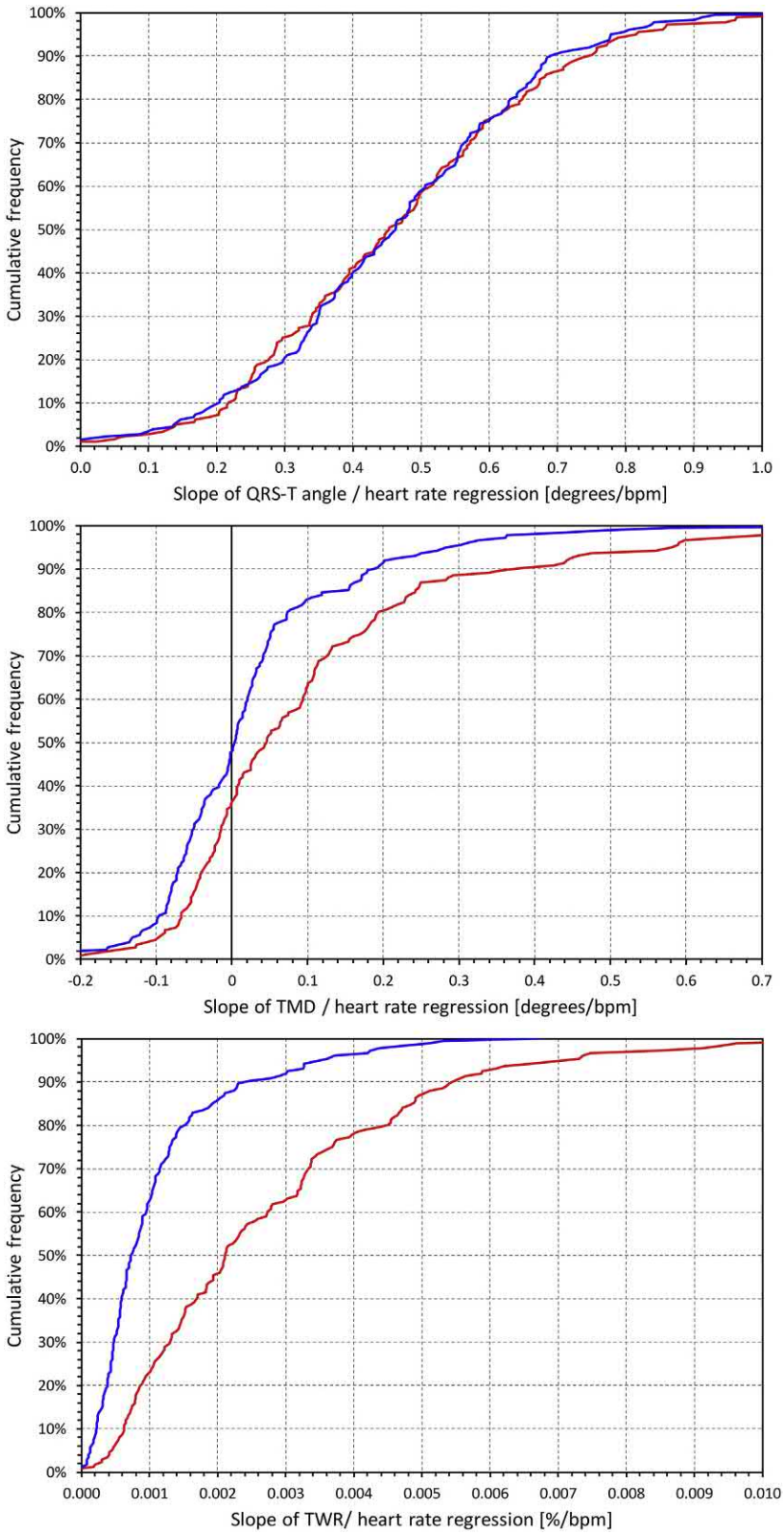

FIGURE 11.8 Cumulative distributions of the slopes of linear regressions between QRS-T angle and the heart rate (top panel), T-wave morphology dispersion (TMD, middle panel), and relative T-wave residua (TWR, bottom panel). In each panel, the *red and blue lines* show the distributions of the slopes in female and male subpopulations, respectively. The values of the slopes are related to the changes of the T-wave morphological indices per heart rate change of one beat per minute (bpm).

Daytime profiles

Circadian patterns of the T-wave morphology descriptors have also been previously reported [22], but it was also shown that these were comparable to the circadian pattern of the underlying heart rates. To confirm this previous observation, daytime profiles of the investigated indices were also researched. Similar to the heart rate bin analysis, the measured indices were grouped in each subject in different parts of the data that belonged to different clock intervals (clock bins differing from the central value of the bin by up to 15 min), and in each of these intrasubject time slices, median value was obtained. The median values were subsequently statistically summarized in female and male subpopulations.

The corresponding analysis of the underlying heart rate is shown in Fig. 11.9. The heart rate patterns shown in the figure reflect the investigative conditions of the source clinical study during which the participating subjects were kept, by protocol, in supine resting positions for most of the morning hours. The corresponding profiles of T-wave morphological indices are shown in Fig. 11.10. This figure shows that to a large extent, the hour-by-hour changes of the indices were predominantly driven by the heart rate changes (i.e., by the combination of the rate dependencies shown in Figs. 11.7 and 11.8 with the heart rate profiles shown in Fig. 11.9). Fig. 11.10 also shows that some other sources of circadian variability might also need to be considered in future investigation of the dynamic properties of these indices.

Interindex relationship

Since the different T-wave morphological indices reflect different facets of ventricular repolarization processes, it is plausible to expect some correlations between their subject-specific values. Nevertheless, when investigating such population-based correlations among healthy subjects, no strong interindex relationships are found.

Fig. 11.11 shows scatter diagrams between the indices measured in individual subjects of the researched population at the heart rate of 80 bpm, i.e., in the middle of the heart rate ranges shown in Fig. 11.7. Apart from obvious sex differences, no systematic relationships are observed. Only T-wave residuum seems to correlate mildly with TMD values in the female subpopulation while among males, only a nonsignificant trend toward such a correlation is found.

Conclusion

T-wave morphology indices show clear sex differences in normal physiologic ECG recordings of healthy subjects. The differences exist in terms of both the absolute measurements in the heart rate dependency of selected morphological indices.

Of the three indices presented in this chapter, spatial QRS-T angles were found approximately 10−15 degrees smaller in females compared to males, but their population spread was substantial with clear overlap between the sex subgroups. In both sexes, QRS-T angles increased with increasing heart rate, but the difference between females

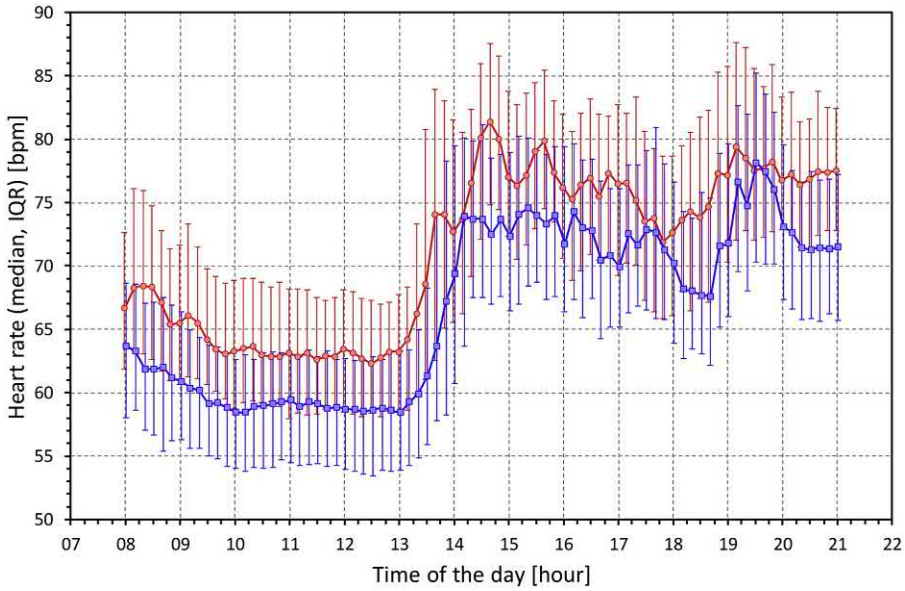

FIGURE 11.9 Development of heart rate during the daytime recordings made in the investigated population of healthy subjects. For each time window (see the text for details), the graphs show the population median heart rate values in beats per minute (bpm); the error bars show the interquartile ranges (IQR). The *red and blue lines* correspond to the female and male subjects, respectively.

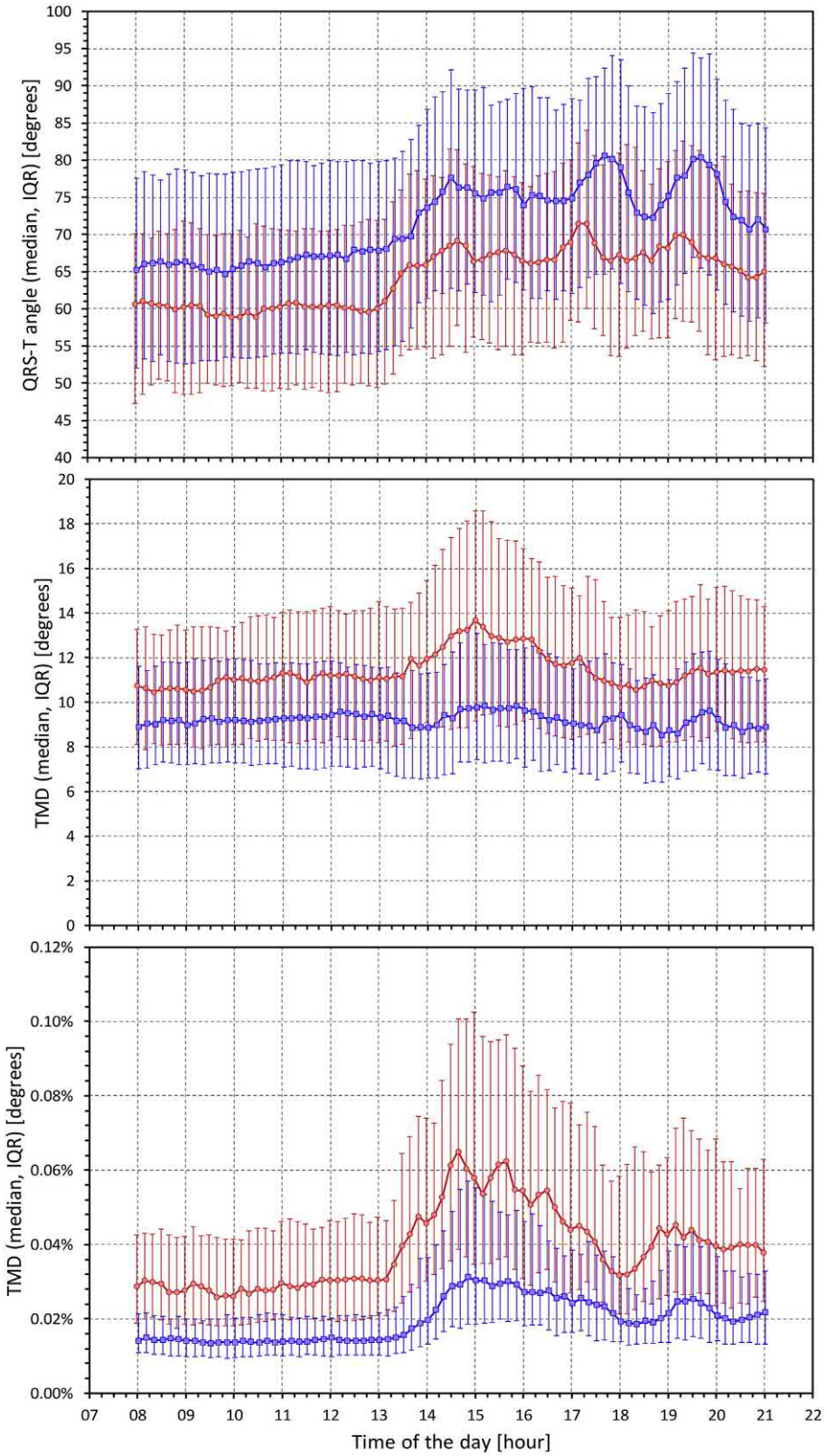

FIGURE 11.10 Development of the T-wave morphological indices during the daytime recordings made in the investigated population of healthy subjects is shown for the QRS-T angle (top panel), T-wave morphology dispersion (TMD, middle panel), and relative T-wave residua (TWR, bottom panel). For each time window (see the text for details), the graphs show the population median values; the error bars show the interquartile ranges (IQR). *The red and blue lines* correspond to the female and male subjects, respectively. Compare with Fig. 11.9.

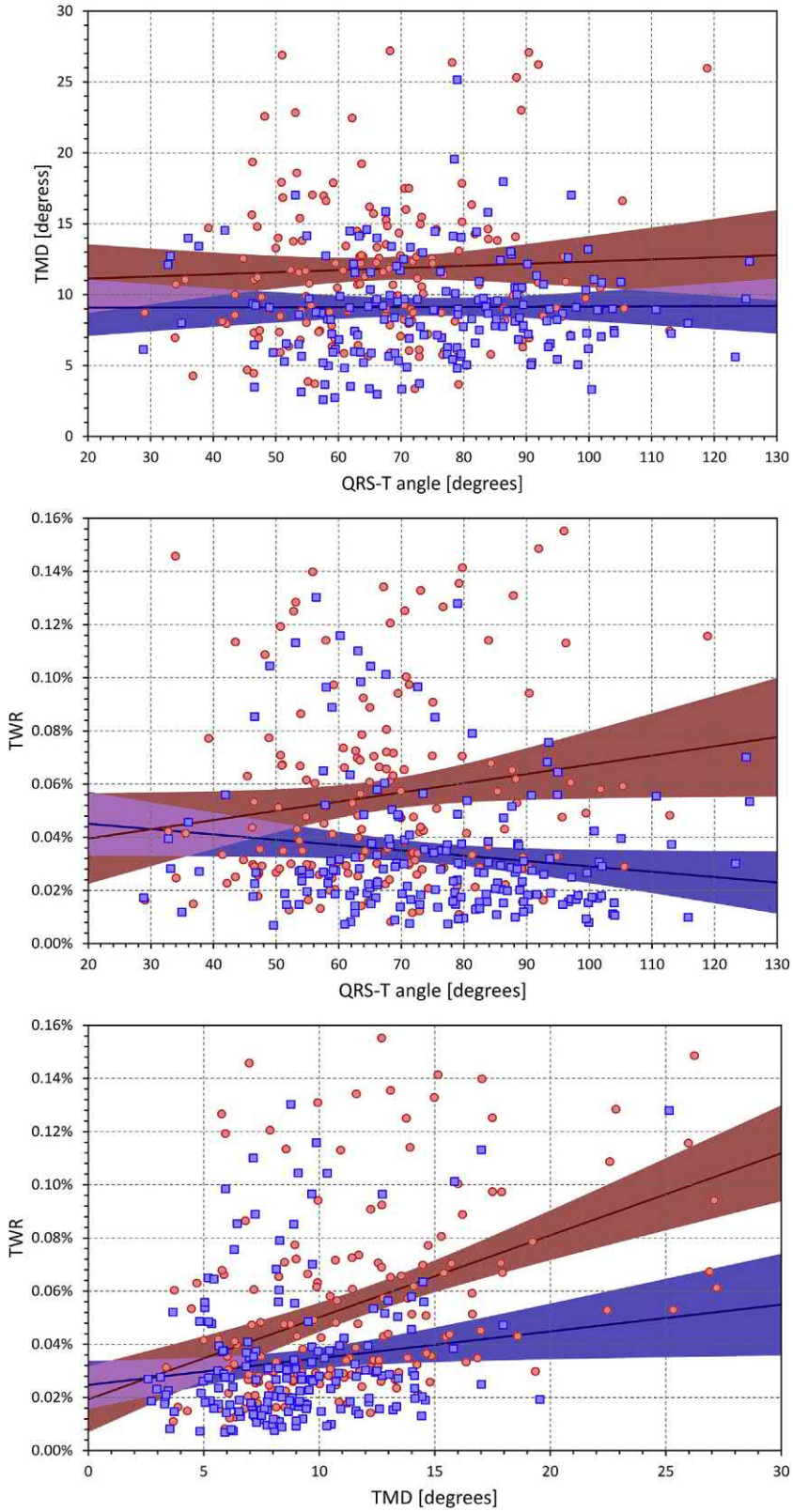

FIGURE 11.11 Scatter diagrams of the relationship between T-wave morphological indices measured in individual subjects at the heart rate of 80 beats per minute. (That is, in each subject, all the measurements of the T-wave morphology indices made at heart rates between 75 and 85 beats per minute were considered and their medians are shown in the panels of the Figure.) The top panel shows the relationship between QRS-T angle and T-wave morphology dispersions (TMD), the middle panel between QRS-T angle and relative T-wave residua (TWR), and the bottom panel between TMD and TWR. In each panel, the *red/pink circles* correspond to female subjects and the *blue/light-blue squares* to male subjects. The *solid red and solid blue lines* show the linear regressions between the displayed indices in females and males, respectively. The red shaded and blue shaded areas are the 95% confidence intervals of the regression lines; the violet areas are the overlaps between the confidence intervals of the sex-specific linear regressions.

and males was practically the same at different underlying heart rates.

TMD showed little heart rate dependency across sex-specific populations although in both sexes, subjects were observed in whom the TMD values increased and decreased with increasing rate. Again, the index showed large spread over the investigated normal population. On average, females showed TMD values approximately 3–4 degrees larger than males.

Despite a large spread of the values in the population, relative T-wave residuals were found substantially larger in females compared to males. In females compared to males, the residuals also increased, on average, approximately twice as fast with increasing heart rate.

Although these normative values were found in normal healthy adult population, the observed sex differences suggest that in clinical studies, which use the T-wave morphological indices for risk and other stratification of patients, sex differentiation should be considered and sex differences of the measurements should be incorporated into the data analyses.

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Chapter 12

Sex-based differences in T-wave alternans

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Introduction

T-wave alternans (TWA), a beat-to-beat fluctuation in the morphology and amplitude of the ST segment or T wave (Fig. 12.1) [1], has proved to be useful in assessing risk for cardiovascular mortality including sudden cardiac death (SCD), which claims >556,000 lives annually in the United States alone [2]. The dire nature of SCD risk is underscored by the fact that in 50% of cases [3], premature demise is the initial manifestation of underlying coronary artery disease (CAD). The main noninvasive indicator of cardiovascular risk, left ventricular ejection fraction (LVEF), has significant limitations as the majority of individuals who die suddenly have relatively preserved LVEF, whereas a high percentage of patients with depressed LVEF do not die suddenly.

The utility of TWA as an SCD risk marker has been studied in >14,000 patients using contemporary methodologies [1]. Multivariate analyses revealed that TWA conveys risk status beyond standard clinical variables for CAD, including demographic factors (e.g., age, sex, and race) as well as cardiovascular risk markers (e.g., smoking, blood pressure, clinical history, and medications) as well as LVEF and other risk indicators. All published clinical investigations were corrected for confounding by these factors. However, relevant to the current topic, the precise correction factors for the influence of sex have rarely been reported.

The objectives of this review are threefold: (1) to summarize briefly the electrophysiology basis for TWA's predictive capacity and the underlying physiologic factors that influence its level; (2) to discuss the contemporary methodologies and clinical evidence supporting TWA's predictive value; and (3) to review available evidence indicating potential sex-related differences in this phenomenon and its measurement.

Synopsis of mechanisms and physiologic influences

TWA's value in estimating risk for cardiovascular mortality and SCD is predicated on its reflection of the degree of heterogeneity of repolarization [4] and of abnormalities in intracellular calcium cycling [5–7], which initiate a beat-to-beat alternation of action potential duration leading to alternating changes in the size and shape of the T wave. TWA can be either spatially concordant, when action potentials in adjoining cell regions alternate in phase, or discordant, when they are out-of-phase. The transition from concordant to discordant TWA heralds increased risk for malignant arrhythmias [4]. Diverse physiologic interventions alter TWA levels consonant with their influence on heterogeneity of repolarization and vulnerability to ventricular tachyarrhythmias (Table 12.1). Surges in heart rate, adrenergic stimuli, behavioral stress, myocardial ischemia, and reperfusion increase TWA levels while also enhancing arrhythmia risk. Conversely, vagus nerve stimulation (VNS), beta-adrenergic receptor blockade, calcium channel antagonism, inhibition of late I_{Na}, and sympathetic denervation, which reduce susceptibility to ventricular tachyarrhythmias, also reduce TWA level.

Clinical methodologies and evidence of predictive capacity

Two main techniques have been cleared by the United States Food and Drug Administration to measure microvolt levels of TWA for risk stratification for arrhythmic death and have been commercialized: the Spectral Method, formerly available through Cambridge Heart, Inc. (Wilmington, MA), and the Modified Moving Average

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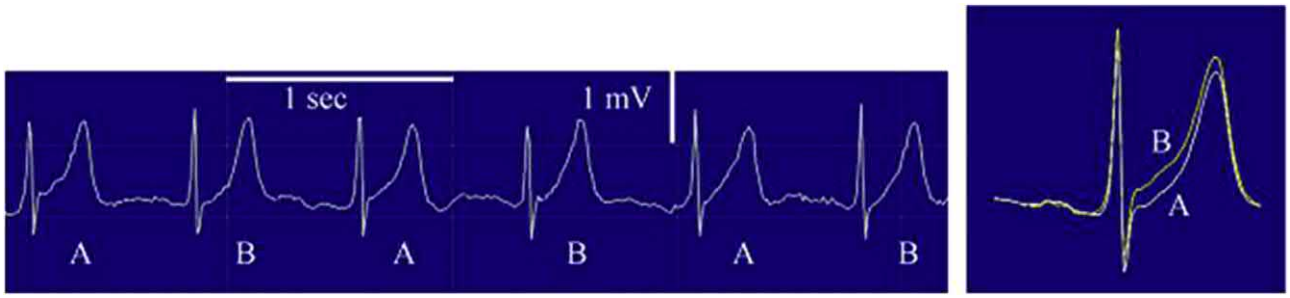

FIGURE 12.1 Precordial (V4) electrocardiogram rhythm strip (left panel) and high-resolution template of QRS-aligned complexes (right panel) during routine exercise tolerance testing from a patient with coronary artery disease who experienced cardiovascular death at 12 months following the recording. The template illustrates T-wave alternans (TWA) as a separation between ST-T segments in A and B beats. TWA magnitude = 106 μV. *Sec*, second. *Reproduced with permission from Verrier RL, Klingenheben T, Malik M, El-Sherif N, Exner D, Hohnloser S, et al. Microvolt T-wave alternans: physiologic basis, methods of measurement, and clinical utility. Consensus guideline by the International Society for Holter and Noninvasive Electrocardiology. J Am Coll Cardiol 2011;44:1309–24. https://doi:10.1016/j.jacc.2011.06.029. PMID: 21920259.*

TABLE 12.1 Physiologic and pharmacologic influences on T-wave alternans: Experimental and clinical correlations.

Experimental interventions	Clinical correlates
Increase TWA	
• Heart rate increases and rapid atrial pacing	Right atrial pacing or exercise increase TWA
• Adrenergic stimuli and behavioral stress	Anger recall and mental arithmetic increase TWA in ICD patients Anger-induced TWA predicts ICD discharge
• Myocardial ischemia	TWA correlates with intraprocedural VT during PCI in STEMI patients (AUC = 0.87) TWA stratifies risk for 1-year mortality in ACS patients
• Reperfusion (initial minutes)	Surge in TWA prior to VT/VF during PCI
• I_{Kr} blockade with E4031	d-sotalol increased arrhythmia in CAD patients; clinical effects on TWA have not been reported
• Flecainide	Produced proarrhythmia in patients with CAD; clinical effects on TWA have not been reported
Decrease TWA	
• Stellectomy	Reduced SCD in long QT syndrome and postmyocardial infarction patients
• Vagus nerve stimulation (VNS)	VNS reduced TWA in patients with epilepsy; VNS reduced TWA and ventricular tachyarrhythmias in heart failure patients
• Beta-adrenergic blockade	Metoprolol reduced SCD in post-MI patients Beta blockade during fixed-rate EP testing or graded exercise decreased TWA
• Calcium channel antagonism	Decreased NSVT and TWA in Prinzmetal's angina patients
• Late I_{Na} inhibition	Decreased VT in MERLIN; case report of ranolazine's parallel suppression of ventricular tachyarrhythmias and TWA

Modified from Verrier RL, Malik M. Quantitative T-wave alternans analysis for guiding medical therapy: an underexploited opportunity. Trends Cardiovasc Med 2015;25:201–13.

(MMA) method (GE Healthcare, Milwaukee WI). Other implementations also exist. The essential elements in the use of these methods are summarized in Fig. 12.2 [1,8].

Among the main differences in clinical applications of these methods is that the Spectral Method was restricted to exercise tolerance testing (ETT) to achieve a fixed target heart rate of 100–110 beats/min and required specialized electrodes. In contrast, with the MMA method, heart rate is allowed to fluctuate and specialized electrodes are not needed. As a result, MMA-based TWA can be utilized not only during routine ETT in the flow of clinical evaluation but also during ambulatory electrocardiogram (AECG) monitoring and was recently shown to be suitable for ECG patch monitoring [9,10].

The odds ratios generated by the Spectral and MMA methods are comparable [1]. The odds ratios for predicting

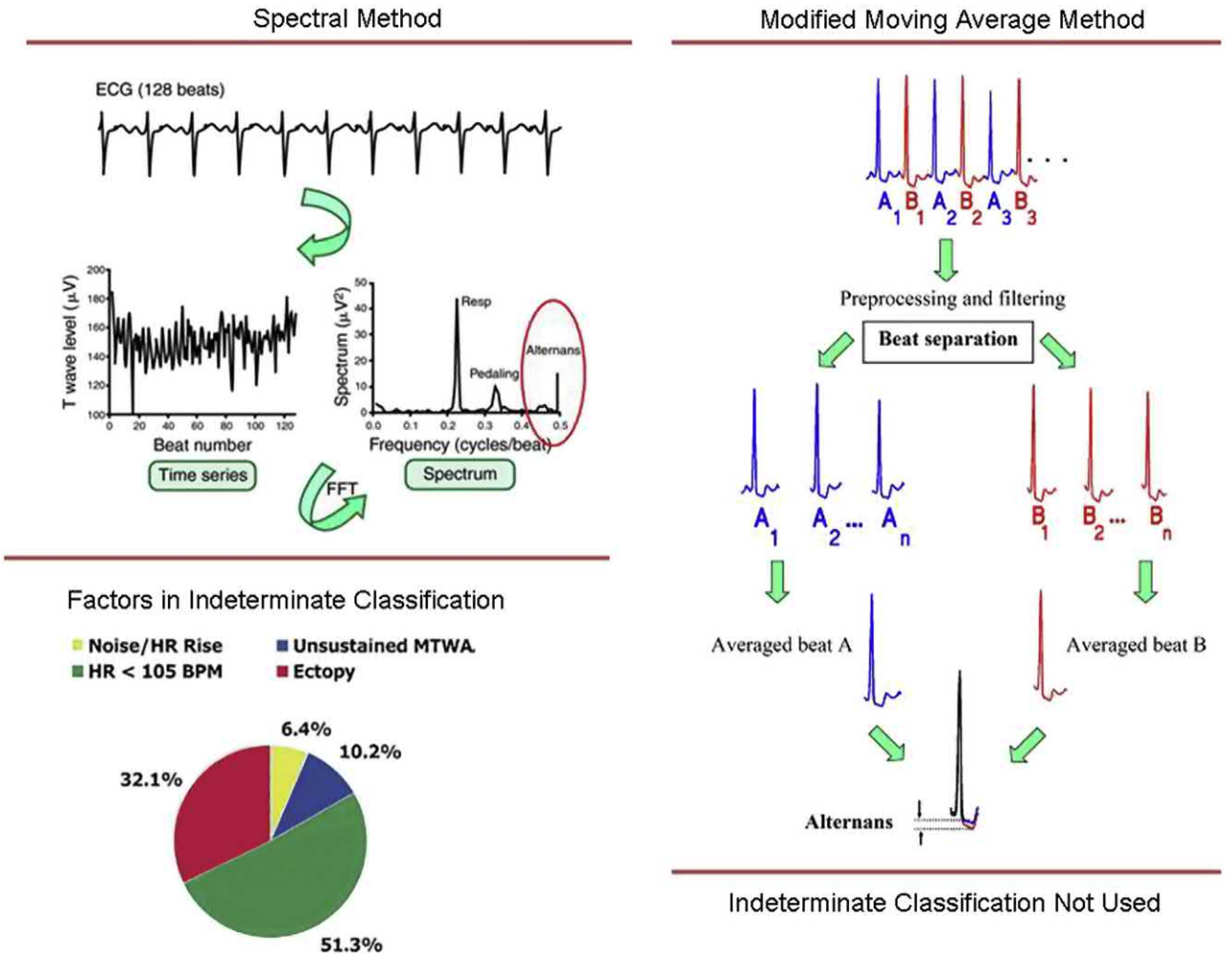

FIGURE 12.2 Left panel, upper figure: Schematic representation of T-wave alternans (TWA) assessment of the electrocardiogram (ECG) with the Spectral Method. This method employs the Fast Fourier Transform (FFT) to estimate the amplitude of the spectrum at 0.5 cycle/beat. The average alternans value across the ST−T wave is reported. Implementation of this method requires raising and maintaining heart rate at 105−110 bpm and records the electrocardiogram (ECG) with specialized electrodes. TWA levels $\geq$1.9 μV with signal-to-noise ratio K = 3 sustained for 2 min are designated a positive test. Results below this level are deemed negative. Left panel, lower figure: Causes of indeterminate microvolt T-wave alternans tests. Only 6.4% of the indeterminate MTWA results were due to technical factors; the remainder was due to patient factors. *BPM*, beats/min; *HR*, heart rate. Right panel: Flow chart of the major components of the Modified Moving Average (MMA) method of TWA analysis. This method employs the noise-rejection principle of recursive averaging [4]. The algorithm continuously streams odd and even beats into separate bins and creates median complexes for each bin. These complexes are then superimposed, and the maximum difference between the odd and even median complexes at any point within the JT segment is averaged for every 10−15 s and reported as the TWA value. The moving average allows control of the influence of new incoming beats on the median templates with an adjustable update factor (i.e., the fraction of morphology change that an incoming beat can contribute). The recommended rapid update factor of one-eighth provides greater sensitivity and capacity to detect transient but clinically important surges in TWA than one-sixteenth or one-thirty second. Noise measurements are in part derived from mismatch of the even or odd median complexes outside the JT segment. The algorithm excludes extrasystoles, noisy beats, and the beats preceding them and filters effects of noise, movement, and respiration. *Reproduced from with permission from Verrier RL, Klingenheben T, Malik M, El-Sherif N, Exner D, Hohnloser S, et al. Microvolt T-wave alternans: physiologic basis, methods of measurement, and clinical utility. Consensus guideline by the International Society for Holter and Noninvasive Electrocardiology. J Am Coll Cardiol 2011;44:1309−24. https://doi:10.1016/j.jacc.2011.06.029. PMID: 21920259.; Kaufman ES, Bloomfield DM, Steinman RC, Namerow PB, Costantini O, Cohen RJ, et al. "Indeterminate" microvolt T-wave alternans tests predict high risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. J Am Coll Cardiol 2006;48:1399−404.*

cardiovascular mortality and SCD in over 300 post-myocardial infarction (post-MI) patients using these two methods proved to be equivalent [11]. The NPV averaged 97.2% for the Spectral Method and ranged from 94% to 99% for the MMA method. For both methods, the PPV was variable, averaging 19.3% for the Spectral Method and 14%−37% for the MMA approach. These findings were attributed to variabilities in population characteristics. Outcomes analyses, however, determined that MMA-based TWA provides additional insight in determining patients'

levels of risk for cardiac events [12] while the Spectral Method did not [13].

A crucial factor that impacted the predictive capacity of TWA analyzed by the Spectral Method is the fact that beta-adrenergic blocking agents, which reduce SCD incidence, were washed out during ETT to meet the heart rate elevation requirement and were reinstated after the test. This protocol design flaw likely accounted in part for the Spectral Method's failure to predict cardiovascular outcomes, as shown in a metaanalysis of high-profile studies [14], which dampened interest in the use of the Spectral Method. By comparison, MMA-based TWA studies are conducted with chronic medications including beta blockers, and all MMA-based TWA studies that employed the methodology correctly have been predictive. Overall, MMA-based TWA appears to be useful not only for risk assessment of both SCD and cardiovascular mortality but also in evaluating anti- and proarrhythmic effects of medical therapy [15] and device-based therapy including VNS [16], as reviewed [17].

Clinical evidence supporting use of quantitative TWA analysis

Quantitative MMA-based TWA analyses on AECG have been found to predict cardiovascular mortality and SCD in patients with a spectrum of cardiac diseases and with varying degrees of left ventricular dysfunction (Table 12.2) [1,17]. Different disease states are associated with a range of TWA levels that correlate with established degrees of risk (Fig. 12.3).

Normal control groups

In healthy newborns, MMA-based TWA levels were reported at 32 ± 8 (range 12–55) μV, and in normal children both male and female from ages 7 to 17, TWA was found to be 30 ± 11 (range 10–55) μV [18]. The range was similar in normal adolescent elite athletes and was related to myocardial mass and history of sports participation but not to sex [19]. In young adults ~21 years of age, TWA averaged 30 (interquartile range 26–37) μV [20]. In adults in their late 50s to early 60s, during the coronary prone years, TWA levels observed for control subjects were 34 ± 11 μV [21] and 37 ± 13 μV [22]. Normal individuals aged ≥65 years enrolled in the Cardiovascular Health Study exhibited TWA levels of 38 ± 13 μV in precordial lead V_5 [23].

Ischemic heart disease

Acute coronary syndrome: Takasugi and colleagues [24] reported on TWA during percutaneous coronary intervention (PCI). TWA level was higher in the 3 patients who experienced ventricular tachyarrhythmias requiring cardioversion during PCI than in the remaining 17 patients, who had no arrhythmias. Visible TWA occurred shortly before the arrhythmia.

ST-elevation myocardial infarction (STEMI): High levels of TWA, i.e., 75.1 ± 6.3 μV, coincided with nonsustained ventricular tachycardia (NSVT) during or following PCI; patients without periprocedural NSVT displayed significantly lower TWA levels, 49.9 ± 3.6 μV ($P < .005$) [25]. TWA ≥60 μV predicted NSVT with sensitivity of 77%; specificity, 73%; positive predictive value, 71%; and negative predictive value, 79%. Area under the receiver operating characteristic curve (AUC) was 0.87 for maximum TWA in predicting NSVT. Importantly, ST-segment levels did not differ in patients with as compared to without NSVT and were not predictive (AUC = 0.52).

Non-ST elevation acute coronary syndrome (NSTEACS): In patients with NSTEACS and LVEF <40%, TWA ≥47 μV early after hospital admission was associated with elevated risk for mortality at 1 year (OR 2.35, 95% CI: 1.03–5.37, $P = .043$) [26].

Postmyocardial infarction

The first investigation of MMA-based TWA was a case–control study of post-MI patients enrolled in the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study [27]. The cutpoint for risk of cardiac arrest or arrhythmic death was set a priori at 75th Percentile of TWA level in patients without events, found to be 47-μV, and is in current use. A 4- to 7-fold higher odds of life-threatening arrhythmias were predicted by TWA values above this criterion. Whereas myocardial infarction often sets the stage for SCD [28], post-MI patients with stable CAD may exhibit low levels of TWA (21.1 μV) during the year following the event, indicating favorable remodeling of the myocardial substrate with recovery of cardiac electrical stability [29].

The postexercise recovery period affords a suitable setting to monitor TWA using AECG recordings [30]. This study validated the 60-μV cutpoint for severe abnormality for MMA-based TWA analysis utilizing the Risk Estimation Following Infarction Noninvasive Evaluation (REFINE) study [11] as a test cohort and the FINnish CArdioVAscular Study (FINCAVAS) database [31] as a validation cohort. A parallel increase in outcomes with higher TWA levels was observed, as each 5 μV of TWA indicated a 5% increase in risk of cardiovascular death.

Hou and coworkers [32] demonstrated in post-MI patients that MMA-based TWA predicted SCD with hazard ratio of 17.78 ($P < .0001$) and moreover that the number of episodes of TWA above the ≥47 μV threshold added significant prognostic information. These investigators

TABLE 12.2 Clinical studies of TWA on ambulatory ECGs with the time-domain modified moving average method.

First author, year (trial)	Patient population (enrollment, disease, mean age)	Mean LVEF	TWA hazard ratios (95% CI), AUC, NVP, and PPV for SCD or life-threatening arrhythmias
Verrier et al. 2003 (ATRAMI) [27]	Acute post-MI; case: control analysis (15 cases: 29 controls) from 1284 ATRAMI patients; 60–62 years	Moderately depressed (42 ± 3%)	4.2 (1.1–16.3, $P < .04$) to 7.9 (1.9–33.1 $P < .005$) for cardiac arrest or arrhythmic death at 21 ± 8 months for a priori 75th %ile cutpoint (47 μV); patients were monitored at 15 ± 10 days post-MI
Slawnych et al. 2009 (REFINE and FINCAVAS) [30]	322 post-MI patients; 62 (interquartile range 53–70) years	Moderately depressed (38%–48%)	3.7 (1.4–9.7, $P = .008$) monitored during postexercise recovery at 10–14 weeks after MI for CV death at 47 months for TWA ≥60 μV; NPV = 95%; PPV = 14%; sensitivity = 20%; specificity = 92%; 2.6 (1.0–6.6, $P = .05$) for SCD. AUC = 0.69
Stein et al. 2008 (EPHESUS) [23]	Acute post-MI, LVEF ≤40%, and heart failure; case: control analysis (46 cases: 92 controls) from 493 EPHESUS patients in AECG substudy; 68 ± 11 years	Depressed (34 ± 5%)	5.5 (2.2–13.8, $P < .001$) for SCD at 16.4 months for 47 μV; patients were monitored at 2–10 days post-MI. For SCD, AUC = 0.73 for lead V_1 and = 0.70 for lead V_3 ($P < .001$)
Sakaki et al. 2009 [39]	295 consecutive patients with ischemic or nonischemic cardiomyopathy and left ventricular dysfunction; 66 ± 16 years	Depressed (34 ± 6%)	17.1 (6.3–46.6, $P < .001$) for CV death, 22.6 (2.6–193.7, $P < .005$) for witnessed SCD at 1.1 year for TWA ≥65 μV; NPV for CV death = 97%; PPV = 37%; sensitivity = 74%; specificity = 87%
Maeda et al. 2009 [60]	63 consecutive patients including 21 controls, 21 post-MI patients without VT, and 21 post-MI patients with VT; 65 ± 11 years	Depressed (36%–43%) for post-MI group	6.1 (1.1–34.0, $P < .041$) for sustained VT or VF at 6 years for TWA ≥65 μV; patients were monitored at 1–3 months after MI
Stein et al. 2010 (CHS) [23]	General population patients ≥65 years old; case: control analysis (49 cases: 97 controls) from 1649 CHS patients; 73 ± 5 years	Not tested, assumed preserved	4.84 (1.48–15.81, $P < .009$) for SCD across 4.7 ± 3.0 (range 0.2–10.4) years for TWA ≥37 μV
Hoshida et al. 2012 [35]	313 consecutive post-MI patients, 70 ± 12 years	48%	3.6 (1.3–10.4, $P < .0174$) for cardiac mortality; 5.8 (1.6–20.8, $P < .0072$) for SCD for TWA ≥65 μV at 3.3 years; patients were monitored >2 weeks after MI
Ren et al. 2012 [22]	173 consecutive post-MI patients with and without diabetes mellitus; 66 years	46%	AUC = 0.708 for cardiac mortality at 1.6 yrs; patients were monitored at 1–3 weeks after MI
Shimada et al. 2012 [21]	40 consecutive patients with vasospastic angina, 59 years	66%	15.5 (1.7–142.0, $P = .009$) for VT at 2.9 years for TWA ≥65 μV during asymptomatic periods
Sulimov et al. 2012 [33]	111 post-MI patients, 64.1 years	46.6%	5.01 (1.5–17.0, $P < .005$) for SCD at 1 year for TWA >53.5 μV at heart rate of 100 bpm, NPV = 93.9%; PPV = 24.4%; sensitivity = 73.3%, specificity = 64.6%; patients were monitored at 2 months to 36 years after MI

Continued

TABLE 12.2 Clinical studies of TWA on ambulatory ECGs with the time-domain modified moving average method.—cont'd

First author, year (trial)	Patient population (enrollment, disease, mean age)	Mean LVEF	TWA hazard ratios (95% CI), AUC, NVP, and PPV for SCD or life-threatening arrhythmias
Hou et al. 2012 [32]	227 consecutive acute (1−15 days) post-MI patients, 56 years	>35% in 201; ≤35% in 18	Hazard ratio = 17.78 ($P < .0001$) for SCD within 16 ± 7 months; hazard ratio = 20.75 (95% CI: 5.8−74.6, $P < .0001$) if ≥ 5 TWA surges ≥47 μV
Verrier et al. 2013 [25]	48 acute STEMI patients; 61 years	51%	AUC = 0.87; NPV = 79%; PPV = 71% for NSVT during or after PCI
Nieminen et al. 2014 (MERLIN) [26]	210 ACS patients, 68 years	<40%	2.35 (1.03−5.37, $P = .04$) for 1 year mortality for TWA ≥47 μV; patients were monitored in-hospital at onset of acute coronary syndrome
Arisha et al. 2013 [61]	199 consecutive post-MI patients, 61.7 years	45%	AUC = 0.64 for SCD or life-threatening ventricular arrhythmias within 6 months; AUC = 0.80 for TWA combined with HRT onset; AUC = 0.86 for TWA combined with HRT onset in patients with LVEF <40%
Summary	• 1793 patients in full-cohort prospective studies • 539 patients in case: control studies	Both depressed and preserved	Range: 2.94−17.1 for cardiovascular death; 4.8−22.6 for SCD

ACS, Acute coronary syndrome; *ATRAMI*, Autonomic Tone and Reflexes after Myocardial Infarction; *AUC*, area under the receive operator characteristic curve; *bpm*, beats/min; *CAD*, coronary artery disease; *CI* = confidence interval; CHS = Cardiovascular Health Study; *CV*, cardiovascular; *EPHESUS*, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; *FINCAVAS*, FINnish CArdioVAscular Study; *HRT*, heart rate turbulence; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *μV*, microvolt; *NPV*, negative predictive value; *NS*, nonsignificant; *PCI*, percutaneous coronary intervention; *post-MI*, postmyocardial infarction; *PPV*, positive predictive value; *REFINE* = Risk Estimation Following Infarction Noninvasive Evaluation; *SCD*, sudden cardiac death; *STEMI*, ST-segment elevation myocardial infarction; *TWA*, T-wave alternans; *VF*, ventricular fibrillation; VT, ventricular tachycardia.
Reproduced with permission from Verrier RL, Malik M. Quantitative T-wave alternans analysis for guiding medical therapy: an underexploited opportunity. Trends Cardiovasc Med 2015;25:201−13.

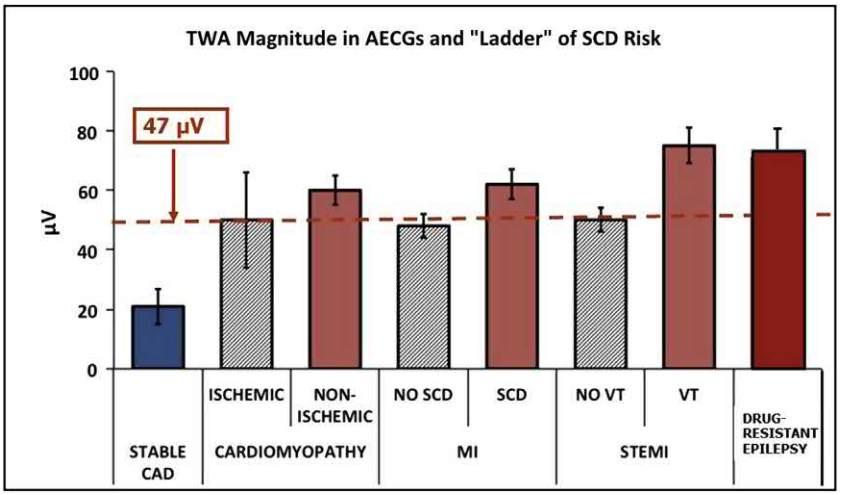

FIGURE 12.3 T-wave alternans (TWA) magnitude determined by Modified Moving Average analysis in ambulatory ECGs showing "ladder" of risk. Mean values of peak TWA are from patients with stable coronary artery disease (CAD), cardiomyopathy, acute postmyocardial (MI) patients with and without sudden cardiac death (SCD), ST-elevation MI (STEMI) patients with and without ventricular tachycardia (VT), and patients with chronic epilepsy. *Modified with permission from Verrier RL, Ikeda T. Ambulatory ECG-based T-wave alternans monitoring for risk assessment and guiding medical therapy: mechanisms and clinical applications. Prog Cardiovasc Dis 2013;56:172–85. https://doi.org/10.1016/j.pcad.2013.07.002.*

reported that the occurrence of ≥5 such surges in TWA indicated enhanced SCD risk, yielding hazard ratios of 20.75 (95% CI: 5.8–74.6, $P < .0001$) on multivariate analysis. Sulimov and colleagues [33] reported evidence that combined analysis of TWA and heart rate turbulence (HRT) [34] in post-MI patients improved prediction, as it increased relative risk for mortality to 28.5 (95% CI: 3.7–172.5, $P < .001$) and for SCD to 58.4 (95% CI: 7.2–474.3, $P < .001$). The largest AECG-based TWA study in post-MI patients was performed by Hoshida and colleagues [35], who enrolled 313 consecutive patients. HRT was independently predictive in this group, and the combination of HRT and TWA improved estimation of cardiovascular mortality risk to 11.4 (95% CI: 4.6–28.6, $P < .0001$) and of SCD to 13.9 (95% CI: 3.0–66.7, $P < .0009$).

There is intriguing evidence that diabetes may augment SCD risk associated with myocardial infarction. Ren et al. [22] reported that patients with myocardial infarction and diabetes exhibited higher TWA levels than did post-MI patients without diabetes (58 ± 21 vs. 52 ± 18 μV, $P < .029$), consistent with their elevated risk for SCD. Combined analysis with HRT [34] generated hazard ratios of 9.08 (95% CI: 2.21–37.2, $P < .002$) for cardiovascular death.

Heart failure

Stein et al. [36] confirmed the MMA-based TWA cutpoint of 47 μV determined in the ATRAMI study [27] in a nested case–control analysis of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). AUC analysis indicated that this TWA level resulted in the most significant separation between hospitalized heart failure patients with left ventricular dysfunction who died suddenly or who survived during the 1.4-year follow-up, with relative risk >5.0. Libbus et al. [16] confirmed that heart failure patients exhibit elevated levels of TWA. Moreover, in the ANTHEM-HF study (NCT01823887), VNS was found to reduce abnormal TWA levels in parallel with tachyarrhythmias.

Sleep apnea in patients with congestive heart failure

Patients with disturbed nighttime breathing, particularly 50% of advanced heart failure patients, have elevated risk for arrhythmias, cardiovascular mortality, and SCD. Takasugi et al. [37] and Yamada et al. [38] reported elevated nighttime TWA levels of 51–65 μV that were significantly correlated with respiratory disturbances in patients with congestive heart failure.

Cardiomyopathy with left ventricular dysfunction

Sakaki et al. [39] performed the initial full-cohort prospective study of AECG-based TWA to examine its predictive strength in patients with either ischemic or nonischemic cardiomyopathy. During the 1.1 ± 0.6-year follow-up, 27 of the 295 patients enrolled died of cardiac causes. TWA analysis yielded significant hazard ratios in both the ischemic (19.0, 95% CI: 6.7–54.2, $P < .0001$) and nonischemic subgroups (12.3, 95% CI: 2.6–58.1, $P < .002$).

Chronic renal disease and hemodialysis

Patients with advanced renal disease necessitating hemodialysis exhibit an elevated risk of SCD. Secemsky et al. [40] investigated TWA in patients undergoing chronic dialysis. The average maximum TWA value for the study period was 71 μV. The TWA criterion level ≥53 μV was reached at least once during the study period by 27 of the 28 patients (96%) and at least twice by 26 patients (92%) during 2 or more 24-h periods. Concomitantly, autonomic disturbances were observed, reflected in heart rate variability (HRV) and HRT. Importantly, hemodialysis did not lower maximum TWA level among >1 year survivors [41].

Epilepsy

The Amsterdam Resuscitation Study [42] and Oregon Sudden Unexpected Death Study [43] revealed that the incidence of death due to sudden cardiac arrest is 3-fold greater in patients with epilepsy than in the general population. These population-based studies prompted investigations to determine whether or not TWA could register cardiovascular comorbidities in patients with chronic epilepsy.

Strzelczyk et al. [44] retrospectively reviewed EKG recordings of 16 patients with complex partial or secondary generalized tonic–clonic seizures and reported that the latter seizures led to a 15-min postictal plateau in TWA. Studies with AECG monitoring reported high TWA levels among patients with chronic epilepsy and moreover that VNS significantly reduced TWA to below the cutpoint of abnormality [45,46]. Most recently, Pang et al. [9] provided evidence that susceptibility to ventricular arrhythmia and abnormal autonomic tone result from cumulative cardiac injury sustained in recurrent seizures. These investigators compared TWA and HRV, both established markers of SCD risk [1,47,48] in patients with chronic as compared to newly diagnosed epilepsy. In this prospective, observational cohort study, patients [newly diagnosed epilepsy, age 41.8 ± 6.8 years; chronic epilepsy, age 40.2 ± 5.6 years ($P = .85$)] were monitored either with a Holter recorder alone or simultaneously with a 14-day Zio XT extended continuous EKG patch monitor. TWA was assessed by MMA analysis; HRV was calculated by rMSSD. TWA levels in patients with chronic epilepsy were significantly higher than in those with newly diagnosed epilepsy (62 ± 5.4 vs. 35 ± 1.3 μV, $P < .002$); the latter did not differ from healthy control adults [21,22]. In all chronic epilepsy patients, maximum TWA exceeded the ≥47-μV TWA cutpoint of abnormality and rMSSD-HRV was inversely related to TWA levels. Patients with chronic epilepsy exhibited TWA levels equivalently on Holter and EKG patch recordings ($P = .38$) with a high correlation ($r^2 = 0.99$, $P < .01$) across 24 h. Based on these observations, it was concluded that chronic epilepsy, the common use of sodium channel antagonists as antiseizure therapy, or other factors are associated with higher maximum TWA levels and simultaneously with lower rMSSD-HRV, which is suggestive of autonomic dysfunction or higher sympathetic tone. Moreover, the study established that the EKG patch monitor used has equivalent accuracy to Holter monitoring for TWA and HRV and permits longer-term EKG sampling. The TWA level observed in patients with drug-resistant epilepsy is compared to major cardiovascular conditions in Fig. 12.3.

Sex-related effects on TWA

The capacity of TWA to register the impact of sex hormones on SCD risk has been underexplored, despite their important influence on repolarization and arrhythmogenesis. Two general applications merit particular attention: (1) sex-related risk for Torsades de Pointes (TdP) in both congenital and acquired forms of long QT syndromes (LQTS) and (2) ischemic heart disease, in which risk for SCD differs among males and females.

Sex hormones and repolarization abnormalities in long QT syndrome

Considerable evidence indicates that female sex constitutes a significant risk factor for TdP in both hereditary and drug-induced LQTS. Numerous reports have documented differences in QTc intervals in healthy individuals and patients with LQT_1 and LQT_2 following onset of puberty [49] (Fig. 12.4). A number of studies have implicated sex-dependent expression of cardiac potassium channels in QT prolongation and arrhythmia risk related to impaired repolarization reserve, which is conducive to unidirectional block and reentry as well as predisposition to triggered activity due to early afterdepolarization. An intriguing new insight into sex-related QT-interval prolongation emerged from a study by Lowe et al. [50]. They employed a mouse model in which the canonical cardiac sodium channel Scn5a locus was disrupted. In a series of elegant experiments, they provided evidence that female myocytes have a significantly larger ventricular late sodium current at baseline than do male myocytes, which predisposes to action potential and QT-interval prolongation. This finding, if verified in humans, would carry important mechanistic and therapeutic implications.

Specifically, in light of growing experimental and clinical evidence that the late sodium current is highly arrhythmogenic, a sex-related enhancement could be construed as a predisposing factor to SCD. This would be the case not only in congenital and acquired LQTS but also in the context of CAD, which is known to enhance the late

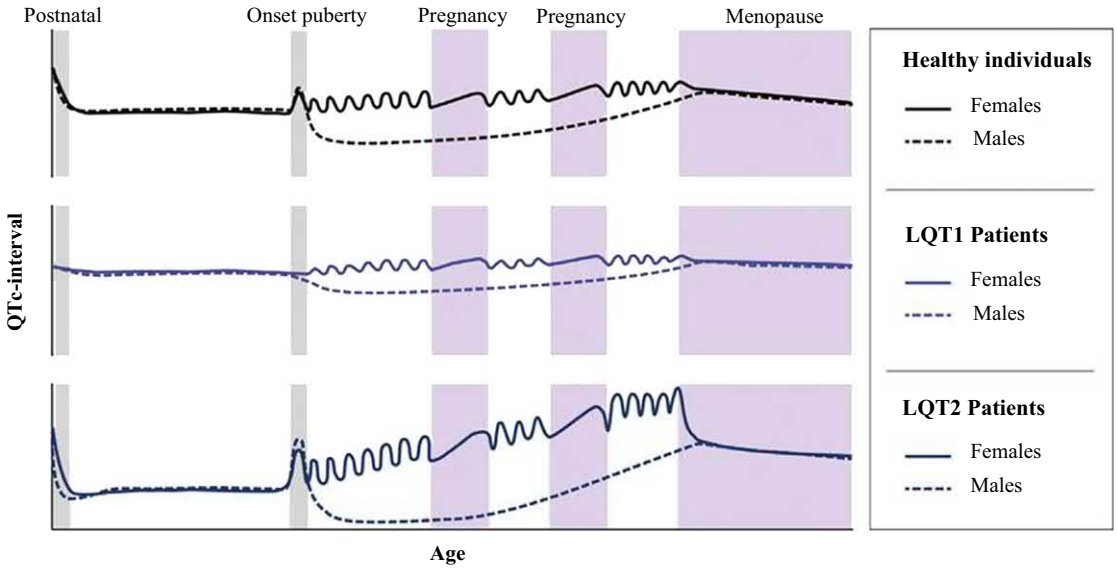

FIGURE 12.4 Schematic representation of hypothetical changes in QTc interval in healthy individuals, LQT1 and LQT2 patients. LQT1 = long-QT syndrome type 1, LQT2 = long-QT syndrome type 2. *Reproduced with permission from Vink AS, Clur SAB, Wilde AAM, Blom NA. Effect of age and gender on the QTc-interval in healthy individuals and patients with long-QT syndrome. Trends Cardiovasc Med 2018;28:64–75.*

sodium current [51]. Potentially therapeutically significant is the fact that nonselective and selective blockers of the late sodium current reduce susceptibility to life-threatening ventricular tachyarrhythmia. In the MERLIN study, inhibition of the nonselective late sodium current by ranolazine was shown to reduce nonsustained ventricular tachyarrhythmias [52]. In experimental studies of acute coronary artery occlusion, both ranolazine [53] (Fig. 12.5) and the selective sodium channel blocker eleclazine [54] were shown to suppress TWA and ventricular fibrillation in parallel.

Quantitative TWA has been demonstrated to be strongly associated with TdP in the three main genotypes LQT1, LQT2, and LQT3 [20] and thus could be helpful in exploring the relationship between sex hormones and risk for this malignant arrhythmia in this and perhaps other channelopathies. A suggestion of an interaction between genetic factors and sex hormones in altering TWA level was provided by Koskela et al. in FINCAVAS [55]. They demonstrated that a common variant, rs10494366, of *NOS1AP* is associated with TWA responses during ETT in a sex-specific manner with a greater increase in TWA in females. However, this allelic variation was not found to be associated with increased mortality.

Sex and TWA in patients with coronary artery disease

The clinical picture of involvement of sex hormones in the setting of ischemic heart disease introduces additional complexities. These relate to the complex countervailing influences on ion channel function and the mitigating factor of atherosclerotic disease. While QT-interval prolongation by female sex hormones has the capacity for enhancing arrhythmogenesis, their influence in retarding atherosclerotic disease would help to delay age-related atherogenesis. It is well established that male sex is associated with increased risk for SCD [2], which would argue that

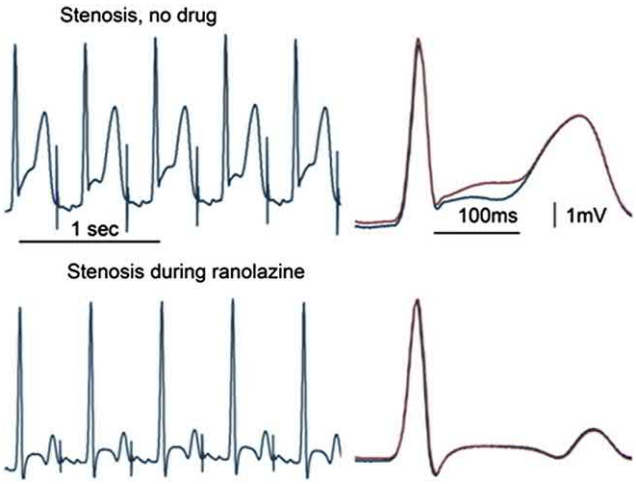

FIGURE 12.5 T-wave alternans (TWA) during left anterior descending (LAD) coronary artery stenosis. The tracings with and without ranolazine are continuous (left panels) and with QRS-aligned superimposition (right panels). The stenosis-induced TWA was suppressed by the nonselective late sodium channel blocking agent ranolazine. *Reproduced with permission from Nieminen T, Nanbu DY, Datti IP, Vaz GR, Tavares CAM, Pegler JRM, et al. Antifibrillatory effect of ranolazine during severe coronary stenosis in the intact porcine model. Heart Rhythm 2011;8:608–14.*

coronary atherosclerosis may be a predominant factor that confers enhanced susceptibility to malignant arrhythmias. At a basic cellular level, sex-based differences in calcium handling have been observed [56,57]. Particularly germane is the fact that overexpression of cardiac Na^+/Ca^{2+} exchanger increases susceptibility to ischemia reperfusion injury in male but not female transgenic mice [56]. This observation is particularly relevant as calcium handling is a key factor in generation of TWA as well as enhanced propensity to arrhythmias [1,58].

However, there is a paucity of information implicating male sex as associated with enhanced levels of TWA. Exceptional in this regard are the studies by Trojnarska et al. [59], who observed in adults with congenital heart disease that male sex is associated with a 10.4 odds ($P = .00002$) of increased microvolt TWA levels on multivariate analysis.

Conclusion

Quantitative TWA has been established as a useful marker of risk for cardiovascular mortality and SCD that is based on sound physiologic underpinnings. This index has been tested in diverse pathophysiologic conditions employing standard clinical test platforms including ETT, AECG, and most recently ECG patches. Despite extensive evidence that sex hormones exert significant influences on ion channels controlling repolarization, the application of TWA as a tool with regard to sex-related SCD risk is sparse and merits intensive exploration.

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Chapter 13

Sex-specific definitions of electrocardiographic abnormalities

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Introduction

Sex-specific differences in electrocardiographic (ECG) abnormalities are well established and should be recognized by the practicing physician. There are baseline heart rate (HR) and HR variability differences among healthy men and women. Furthermore, ventricular depolarization and repolarization manifest on the 12 lead ECG as QRS and ST intervals have been the best described changes. These sex-specific ECG patterns form the basis of disease predilection for both sexes. QT intervals are longer in women and ST height is greater in men. Thus, long QT syndrome (LQTS) is more common in females, whereas ventricular early repolarization (ER) pattern, J-point ST elevation, as well as Brugada syndrome (BS) are more common in males. We will describe in detail these ECG differences, as well as the likely physiologic mechanisms for such differences.

Sinus rate

Sinus rate differences among men and women are a well-recognized entity since the initial description of corrected QT intervals in 1920 by Bazett, when it was noted from the data that men have a slower HR than women [1]. Other observational studies have confirmed this finding [2,3]. One physiologic explanation is that stroke volume (SV) is smaller in women than in men and to maintain adequate cardiac output (CO) baseline HR remains higher in women (as the CO = SV × HR) [4]. After accounting for the larger body surface area (BSA) in men when compared to women, the SV was about 10% smaller and HR similarly greater in females resulting in similar cardiac index (CO/BSA) among men and women [2,5]. The slower HR in men is also explained by higher exercise capacity. In addition, healthy women are more vulnerable to orthostatic hypotension in response to changes in body position and have a higher HR response when compared to healthy men [4,6]. Burke et al. [3] illustrated in a cohort study of healthy men (20) and women (23) between the ages of 21 and 39 years that men had a longer sinus cycle length at baseline. They also found a lower intrinsic sinus rate in men, measured after double autonomic blockade, caused by propranolol 0.2 mg/kg and atropine 0.04 mg/kg. All subjects were studied three times, males 5−10 days apart and females during each phase of the menstrual cycle: menstrual, follicular, and luteal phase. Mean sinus cycle length at baseline and mean intrinsic sinus rate were significantly longer in men compared to women (971 ± 88 ms vs. 918 ± 115 ms, $P < .02$; and 645 ± 41 ms vs. 594 ± 57 ms, $P < .0001$, respectively) [3] In addition, in females, the HR at baseline was longer during menstrual phase than the follicular or luteal phase ($P<.03$), but after autonomic blockade there was no difference in HR among all three menstrual phases. Of note, while body mass index (BMI) was similar between groups, the BSA was significantly larger in men ($P<.001$). The subjects also underwent bicycle ergometry exercise and men had a significantly greater maximum exercise capacity than women (1295 kpm vs. 857 kpm, $P<.0001$). Based on multiple regression analysis, sex was the only independent predictor of maximum exercise capacity ($P<.003$), while weight and BSA had no effect [3]. These findings taken together suggested that the difference in HR between the sexes appeared to be related to exercise capacity, rather than any intrinsic sex-based differences in autonomic tone or intrinsic sinus node properties. Additionally, Taneja et al. found a longer baseline sinus cycle length, as well as a longer sinus node recovery time on invasive electrophysiology study (EPS), in men compared with women. This finding was not altered when age was taken into account [7].

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Repolarization: St segment, J point, and J waves

The summated action potential (AP) duration (APD) of the entire ventricular myocyte mass creates electrical activity that is detected on the ECG as the QT interval. Briefly, the AP is created by many channels that transport different ions at different times during the electrical cycle. The rapid upstroke of the AP, phase 0, is cellular depolarization due to the fast activating and inactivating Na channels (SCN5A), which is rapidly followed by phase 1 (ER) and is maintained via the transient outward K+ current (Ito) and inward Cl-current; phase 2 is the plateau phase of repolarization, which is primarily maintained by L-type Ca + channels inward flow and outward K+ flow. The repolarization phase 3 is due to outward K+ movement via multiple potassium channels (IKs/IKr/IKur) (Fig. 13.1) [8,9].

There are differences in ST segment depression during exercise stress testing (EST) between women and men. At 3 min of EST in 204 asymptomatic subjects, ST depression was present in 16% of women and 3% of men [10]. Thus, ST segment depression during EST in females often is a normal variant and has lower sensitivity and specificity in identifying coronary disease when compared to males. In a metaanalysis of symptomatic females with intermediate risk for coronary artery disease, sensitivity and specificity of ST depression during EST was 61% and 70%, respectively [11]. Whereas in a metaanalysis of symptomatic male participants that underwent EST, the sensitivity and specificity of ST depression for identifying CAD was 68% and 77%, respectively [12]. Furthermore, the positive predictive value of ST segment depression during EST of symptomatic men and women who subsequently underwent coronary angiogram was significantly lower in women than in men (47% vs. 77%; $P<.05$), while the negative predictive value of ST segment depression was similar between women and men in ruling out CAD (78% vs. 81%, respectively) [13]. Hence, there is more false-positive ST segment depression during EST in women when compared to men. It is worth noting that the absence of ST depression during EST is similarly useful in both males and females in excluding CAD.

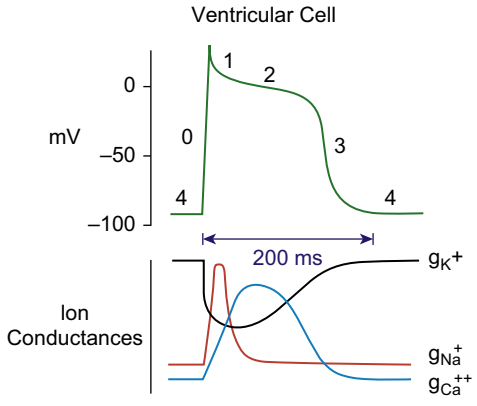

FIGURE 13.1 Ventricular action potential duration consists of four phases, membrane potential regulated via the ion flow via membrane ion channels. *Image courtesy of Dr. Klabunde (https://www.cvphysiology.com/).*

There is plausibility of correlation between estrogen and the ST depression in women during EST. A study of postmenopausal women, who eventually had normal coronary angiogram, showed that women on estrogen replacement therapy had more ST depression during EST when compared to those that were not [14]. In addition, a study of premenopausal women with no CAD showed that ST depression during EST varied with menstrual cycle [15]. These findings taken together suggest that estrogen enhances ST depression.

The ER ECG pattern, more specifically, J-point elevation (JPE), is prevalent in the general population in up to 13% of normals, and over 75% of ER occurs in men [16]. ER pattern is defined as JPE (sharp positive deflection or notch immediately following positive QRS complex at the onset of the ST segment, or presence of slurring of the terminal part of the QRS) ≥ 0.1 mV in two adjacent leads. The ER pattern on ECG with a history of ventricular fibrillation (VF) or sudden cardiac death (SCD) constitutes a diagnosis of ER syndrome. Risk stratification of patients with ER pattern is not well defined and remains a clinical challenge since the occurrence of SCD/VF is rare in these patients. The incidence of idiopathic VF with an ER pattern is low with an estimated absolute risk for arrhythmic death of 70 per 100,000 in a metaanalysis [17]. The ER pattern that is associated with a higher incidence of SCD is defined from multiple retrospective review studies as horizontal/descending ST elevation ≥ 0.1 mV within 100 ms after the J point. An ER pattern in inferior/inferolateral leads as well as longer J-wave duration with wider J-wave angle has a stronger association with idiopathic VF [17].

The amplitude of the J point and the angle between the ST segment and the baseline are also significantly more pronounced in males than females. The reference values for normal healthy males and females were defined in two studies as follows: Male Pattern JPE >0.1 mV in precordial leads V1−V4 and when the ST angle was >20 degree in at least one of these four leads. The Female Pattern J-point amplitude was <0.1 mv, and ST angle was <20 degree (Fig. 13.2) [18]. In a study of 529 healthy males and 544 healthy females, age 5- to 96-year-old, subjects were subdivided into nine age groups. ECG pattern differences among both sexes were statistically significant when combined for all age groups ($P<.001$), although for the oldest age group the differences were borderline ($P = .059$) [18,19]. In females, the Female Pattern was distributed similarly from puberty to advanced

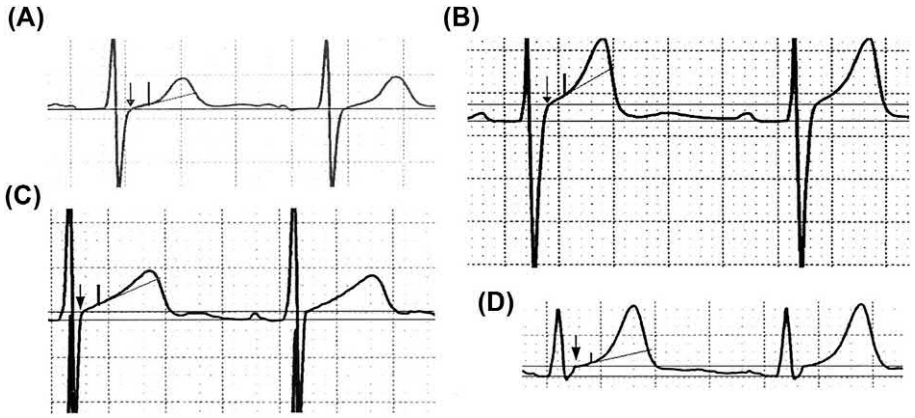

FIGURE 13.2 Method of male and female pattern determination in electrocardiogram complexes of lead V3. The two parallel horizontal lines at the level of Q wave and the J point, respectively. The arrow marks the J point. The short vertical line marks the point 60 ms after the J point; the *oblique line* connects the J point with the *vertical line* point. (A) Female pattern: the J point is at the level of the Q line and the ST angle is 19 degrees. (B) Male pattern: the J point is >0.1 mV above the Q line, and the ST angle is 36 degrees. (C) Variant of the male pattern in which the T wave ascends at the J point; the J point is > 0.1 mV above the Q line, and the angle between the line parallel to the Q line at the level of the J point and the ascent of the T wave is 29 degrees. (D) Indeterminate pattern: the J point is > 0.1 mV above the Q line, and the ST angle is 15 degrees. *From Surawicz et al., Prevalence of male and female patterns of early ventricular repolarization in the normal ECG of males and females from childhood to old age. Journal of the American College of Cardiology 2002;40(10):1870–76.*

age with about 80% prevalence in all ages. However, there is some variation in ECG pattern distribution in female children less than 7 years old. The ECG pattern in males was more variable across age groups, with increasing Male Pattern prevalence up to 91% in the 17- to 24-year-old age group, and declined gradually with advancing age to 14% in the oldest group (Fig. 13.3) [18]. An observational study of 1237 young healthy subjects, age 13–38 years, showed that JPE was significantly more prevalent in males when compared to females (20% vs. 12%, $P = .003$). It is also important to note that JPE is commonly seen in healthy young athletes, and its prevalence is significantly higher in Afro-Caribbeans compared to Caucasians (40% vs. 17%, $P = .0013$) in this particular study [20].

These physiologic differences in ventricular repolarization are most strongly influenced by changes in the availability or activity of the male sex hormones. The age-dependent changes of the Male Pattern JPE appear to parallel the rise of testosterone blood levels during puberty and the young adult years. Additionally, a decrease in the incidence of the Male Pattern was noted with the decline of testosterone levels in elderly males (Fig. 13.3) [18,21]. The mean JPE in healthy adults was also shown to be higher in men compared to women in all ECG territories. McNamara and colleagues studied multiple sex hormone plasma level analyses and their effect on JPE [22]. In this cross-sectional study of 475 healthy males (56%) and females, regression analysis showed that the Estradiol level was an independent predictor of JPE in the inferior leads (B = +1.2 uV change in JPE with every pg/mL change in hormone level, $P<.03$) and free testosterone index level was an independent predictor of JPE in lateral leads (B = +0.01, $P<.05$). Total testosterone level was an independent predictor of JPE in anterior leads in women (B = +0.054, $P<.05$) [22].

Ventricular repolarization time in castrated males was longer than in normal males, and in virilized women was shorter than in normal women, further supporting the role of androgens in AP repolarization phases. Furthermore, it is reported that Male Pattern JPE was restored in three castrated males who received intramuscular testosterone therapy [23]. Testosterone also has effects on duration of repolarization [24,25], which will be discussed below.

BS is another disease causing VF and SCD that shows sex predilection [26], being 8 to 10 times more common in males than females. The classic Brugada ECG phenotype is a coved, descendant ST segment elevation $\geq$ 2 mm in at least one of the right precordial leads (V1–3) followed by a negative T wave. This is termed a type-1 Brugada pattern and is the only one diagnostic for BS. Other forms of Brugada pattern are described as type 2: ST elevation also equal to or greater than 2 mm, but with a saddleback appearance ST elevation and positive or biphasic T waves in V1–V3; and type 3: ST elevation that is <1 mm and can be either cove or saddleback ST elevation, Fig. 13.5 [27,28]. There is compelling data to show that type-1 Brugada ECG pattern, as well as SCD, or VF (spontaneous or induced during EPS) is more common in males [29–34]. A prospective study of BS patients with mean follow-up of 58 months showed that males had increased risk of initial presentation with SCD by 7.4 (CI 1.0–55.5) at the time of diagnosis. Spontaneous type-1 ECG pattern was higher in males, 2.9 (CI 1.8–4.8); also inducibility of ventricular arrhythmia during EPS was increased by 3.5 (CI 1.8–6.9) in males. Genetic mutations related to BS, both SCN5A and GPD1-L genes, show equal inheritance in both sexes, despite that there is male predominance in phenotypic expression of the disease [34].

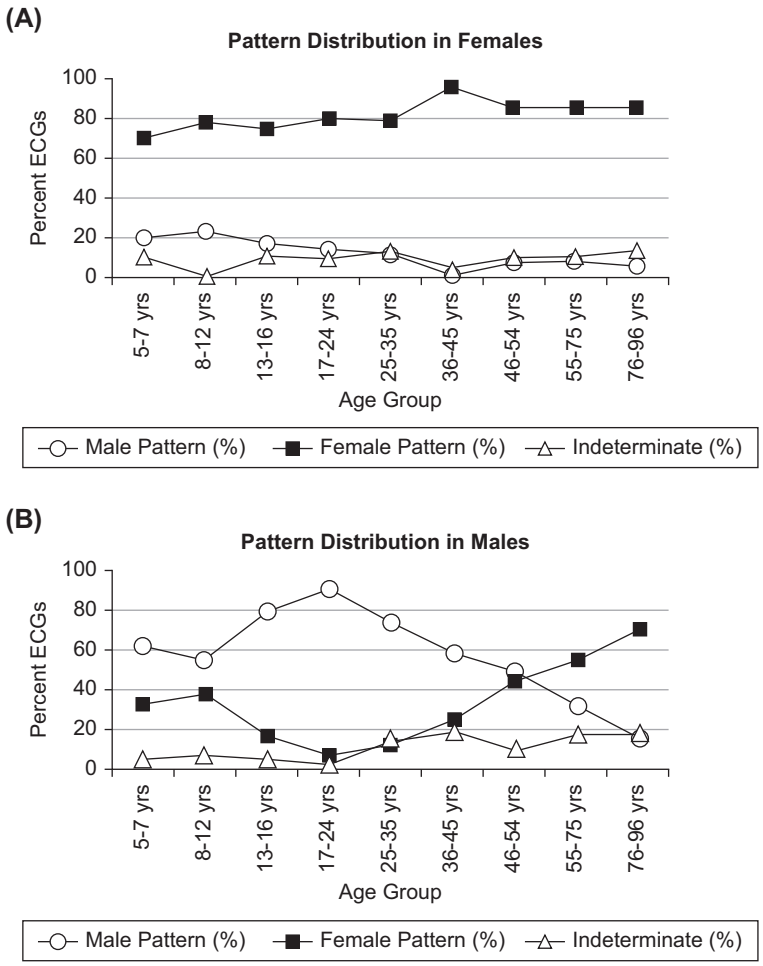

FIGURE 13.3 Early repolarization ECG pattern, J-point ST elevation pattern distribution in different age groups of healthy females (A) and males (B). *From Surawicz et al., Prevalence of male and female patterns of early ventricular repolarization in the normal ECG of males and females from childhood to old age. Journal of the American College of Cardiology 2002;40(10):1870–76.*

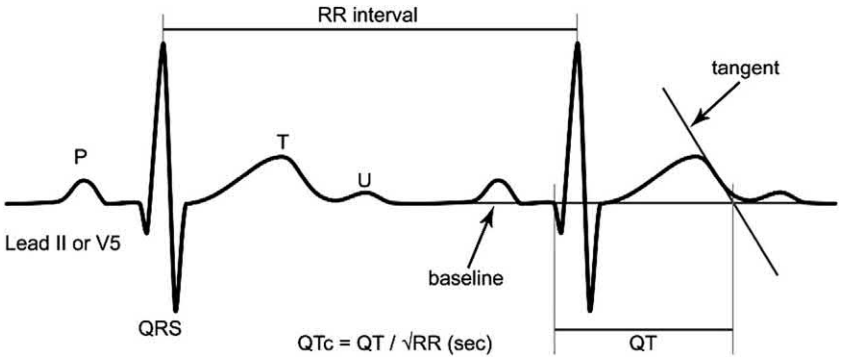

FIGURE 13.4 Accurate measurement of QT interval with presence of U wave and biphasic T wave. *From Postema et al., Accurate electrocardiographic assessment of the QT interval: Teach the tangent. Heart Rhythm 2008;5(7):1015–18.*

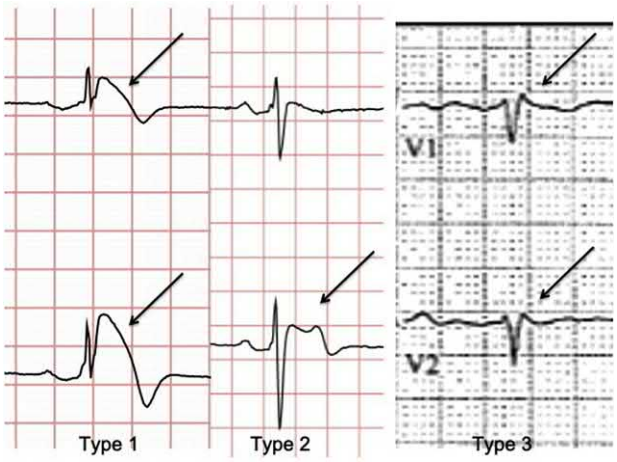

FIGURE 13.5 Brugada Patterns: The left panel displays a type-1 Brugada pattern in leads V1 and V2. Note the concave >2 mm ST elevation and T-wave inversion. The middle panel shows a type-2 (saddleback) pattern in lead V2. The right panel shows a Type-3 pattern with <1 mm ST elevation in leads V1−2 with incomplete right bundle branch block and T-wave inversions.

The physiologic explanation for sex distinction of the Brugada phenotype remains to be proven, but the most plausible explanation is that males have increased density of Ito in the epicardial myocytes of the right ventricle. Thus, males have a deeper notch of AP phase 1. This was illustrated in a canine study of transmembrane potential of epicardial tissue of male and female hearts. The amplitude of phase 1 of epicardial tissue of both male and female canine hearts is shown during baseline cycle length (BCL) of 300, 500, 800, and 2000 ms (ms) (Fig. 13.6A and B). Also, the average rate−dependent amplitude and voltage of phase I of epicardial APD of both sexes is shown (Fig. 13.7C) [35]. Phase I amplitude is significantly smaller in males in comparison to female canine hearts (60.8 mV vs. 73.2 mV) at a BSL of 2000 ms, and, respectively, the voltage at end of phase I is more negative in males than females (−26.2 mV vs. −12.9 mV), Fig. 13.7C. The rate-dependent amplitude of AP phase I is most likely a function of relatively slow recovery of Ito channels from an inactive to an active state, hence at longer BCL there is more outward K+ current via more available Ito channels causing greater repolarization current. Therefore, phase 1 amplitude is smaller at longer BCL. Loss of the AP dome in the epicardium but not the endocardium results in the development of a marked transmural dispersion of repolarization and refractoriness, responsible for the development of a vulnerable window during which a premature extrasystole can induce a reentrant arrhythmia. More specifically, conduction of the AP dome from sites at which it is maintained to sites at which it is lost causes local reexcitation via a phase 2 reentry mechanism, leading to the development of a very closely coupled extrasystole, which captures the vulnerable window across the myocardial wall, thus triggering a circus movement reentry in the form of VT/VF [36]. Furthermore, the loss of the AP dome in LV epicardial tissue is due to the heterogenous distribution of Ito channels in males, as shown in Fig. 13.7 [35].

The influence of testosterone on the BS phenotype has been reported. In addition, there are two reported cases of

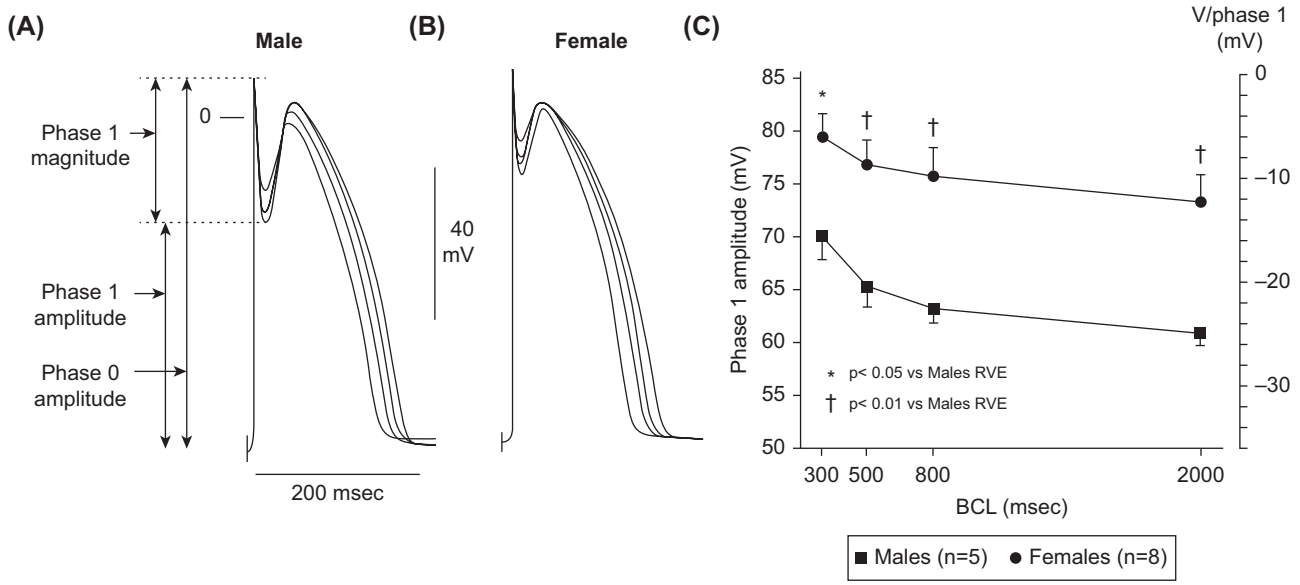

FIGURE 13.6 Transmembrane action potentials recorded from isolated canine RV epicardial male (A) and female (B) tissue slices. Baseline cycle lengths 300, 500, 800, and 2000 ms. (C) Rate dependence of phase 1 amplitude and voltage at end of phase 1 (V/phase 1, mV) in males (*solid squares*) versus females (*solid circles*). *From Di Diego et al., Ionic and Cellular Basis for the Predominance of the Brugada Syndrome Phenotype in Males. Circulation 2002;106(15):1015−8.*

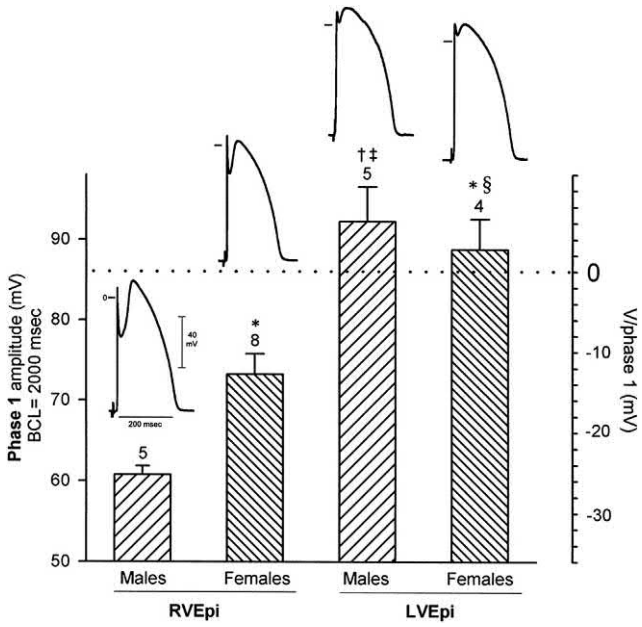

FIGURE 13.7 Phase 1 amplitude and voltage at end of phase 1 (V/phase 1) of epicardial action potentials recorded from male and female tissue slices from RV (RVEpi) and LV (LVEpi) of canine hearts (baseline cycle length = 2000 ms). *From Di Diego et al., Ionic and Cellular Basis for the Predominance of the Brugada Syndrome Phenotype in Males. Circulation 2002;106(15):1015–8.*

asymptomatic Brugada pattern with typical ECG manifestation that diminished after surgical castration treatment for prostate cancer [37]. Subsequently, another study compared 48 male patients with BS to matched control males. BS patients were found to have significantly higher testosterone level, lower BMI, and lower body fat percentage when compared to controls, further supporting correlation of male predominance in BS [37,38].

QT interval

Perhaps the most established ECG difference between men and women is that of the QT interval. A prolonged QTc interval is typically defined as >450 ms in males and >460 ms in females. In clinical practice, an ECG with QTc >480 ms in females and >470 ms in males warrants further investigation. For patients who present with long QTc, offending medications (including antiarrhythmic drug (AAD) and other medications as well as illicit drugs) and electrolyte imbalances such as hypokalemia, hypocalcemia, and hypomagnesemia should be excluded first [39]. One should refer to the following website www.crediblemeds.org for a detailed list of drugs that can prolong the QT. Some of the common QT prolonging medications include antimicrobials (fluoroquinolones, erythromycin, clarithromycin, ketoconazole, itraconazole); antidepressant (fluoxetine, sertraline, doxepin, amitriptyline); antipsychotics (haloperidol, quetiapine, thioridazine); and other well-known QT prolonging drugs are ondansetron, sumatriptan, cisapride, and methadone. Confirming a prolonged QTc is best done with the ECG leads II, V5, or V6 or the lead with longest QT interval. In the presence of a U wave, to accurately measure QT and not overestimate, a tangential line in drawn on a downslope of the T wave to the baseline(Fig. 13.4) [40]. If the T wave is biphasic, and the negative portion is higher amplitude than positive portion, then the measurement is taken to the end of biphasic T wave. Several formulae have been developed for correction of the QT interval, most commonly, Bazetts formula. The RR interval between the measured and the preceding complex is used to obtain the corrected (QTc) interval for both the Bazett ($QTc = QTms/\sqrt{RR\ sec}$) and Fredericia ($QT_C = QTms/RR\ sec^{1/3}$); also QTc can be calculated by using the Hodges formula that is based on QT and $HR(QT_C) = QT + 1.75\ (HR-60)$ [40].

The QTc interval has proven to be significantly different between men and women. This has been shown in multiple studies and is perhaps the more prominent ECG difference in comparison to other electrophysiologic sex differences. It has been established that most of the changes contributing to the longer QT duration in women occur during the ST segment and the beginning of the T wave [41,42]. The QTc interval is approximately 10 ms longer in the female population when compared to the male population [43,44]. QTc sex differences are present mainly after puberty [25,43]. The human ventricular myocytes isolated from failing hearts from female and male patients showed longer APD in females compared to males due to smaller Ito channel flow, reduced phase 1 of APD and prolonged phase 2, less transient outward K+ flow, and larger L-type Ca++ current in females [45–47]. A study of intracellular calcium cycling from epicardial LV cells of rat hearts showed significant differences in calcium cycling properties between males and females, with more rapid calcium release in males and a longer recovery time for females. This study demonstrated that the magnitude of calcium influx, the total amount of calcium released, and the maximum calcium release rate were greater in males, whereas the rise time was shorter in males. In contrast, all characteristics relating to calcium flow duration were prolonged in females, including transient durations at 50% and 90% of total recovery, maximum rate of transient decay, decay time, and peak width [47].

Another study focused on differences in ion current densities among males and females based on animal data and implementation of human ventricular cell mathematical models. Results showed that female cells have longer APD, steeper APD to HR relationship, larger transmural APD heterogeneity, and higher susceptibility to early afterdepolarization (EAD)-triggered arrhythmia than male cells.

Differences in APD were related to disparities in ion-channel density between both sexes, increased density of L-type Ca++ current, decreased density in Ito current, and decreased density of Ikr in females when compared to males. Females exhibit limited repolarization reserve, thus vulnerability to EADs and Torsades de pointes (TdP); Males, by contrast, have limited depolarization reserve and are thus susceptible to all or none repolarization and vulnerability to tachyarrhythmias related to BS. This is related to higher Ito current in the male AP and lower L-type Ca++ current [48]. There is also a molecular basis supporting the disparities in human cardiac repolarization between both sexes. Quantitative gene expression of 79 genes encoding ion channel and transporter subunits in epicardial and endocardial tissues sampled from healthy cardiac transplant donors (10 male and 10 female) was studied; female hearts showed reduced expression for a variety of K+ channel subunits important in cardiac repolarization, including HERG, mink, Kir 2.3, Kv1.4, KChIP2, SUR2, and Kir6.2 [49].

Drug-induced QTc prolongation was greatest in women during the menstrual and ovulatory phases than during the luteal phase and was greater when compared to men [50]. Furthermore, the variability in QTc interval is greater in trials with all female patients when compared to mixed trials. Although these studies used different drugs, QTc variability was compared only for the drug arms that proved not to prolong QTc: Tadalafil (a phosphodiesterase 5 inhibitor, used in males to treat erectile dysfunction) arm in males and Duloxetine (a potent dual inhibitor of serotonin and norepinephrine uptake for treatment of depression) arm in females. Females had larger intersubject and intrasubject QTc variability than males [51]. Another cohort study of 1897 patients (26% women) of the AAD Sotalol found that drug-induced ventricular repolarization prolongation was more prominent in females, for dosing condition of Sotalol 320 mg/day, mean ± SD JTc for women was 329 ± 35 ms and for men was 319 ± 38 ms ($P = .0001$). Multiple regression analysis showed that women exhibited 6.7 ms greater mean prolongation of JTc than men ($P = .003$) [52].

Multiple studies have also demonstrated these differences among healthy athletes. ECGs of more than 600 athletes during preparticipation exam (54% male; mean age, 19 ± 1 years) representing 22 sports, analyzed by computer, showed that male athletes had significantly greater QRS duration, Q-wave duration, J-point amplitude, and T-wave amplitude, but shorter QTc interval compared with female athletes (all $P < .05$). ECG indicators of left ventricular electrical activity were significantly greater in males, with or without LV hypertrophy; QRS duration and voltage were greater when compared to females [53,54]. In another study of athletes, resting ECGs showed that females had a significantly higher HR, shortened conduction time, QRS, and prolonged QTc when compared to males [55,56]. In a prospective study of healthy individuals from the Atherosclerosis Risk In Communities group, 8676 white and African-American subjects, age 40−65 years, showed that QTc was longer in women compared to men in both races (mean QT was 435 ms in men and 445 ms in women of both races combined, $P < .001$). This study demonstrated that epicardial ventricular repolarization in males had earlier onset and offset of repolarization when compared to females, thus resulting in shorter QTc in men [44]. Furthermore, in an observational study of highly trained athletes in Great Britain, 1378 subjects, mean age 21 ± 5 years (55% males and 81% Caucasian) were divided in 2 groups. Group 1 included those with training-related ECG pattern such as isolated LVH, ER patterns (ST elevation >0.1 mV), and first-degree AV block. Group 2 included those with changes not typically related to training; T-wave inversions in leads V1−V4, or inferior leads II, III, aVF. Males had significantly higher prevalence of group 1 (89% vs. 61%, $P = <0.0001$) and group 2 ECG changes (26% vs. 16%; $P = .0001$) compared to females. However, T-wave inversions in anterior leads V1−V4 were more prevalent in female athletes (12% vs. 4%, $P = .0001$). Males also demonstrated higher prevalence of axis deviation (6.7% vs. 2.1%, $P = .0001$), atrial enlargement (4.2% vs. 1%, $P = .0002$), and right ventricular hypertrophy (8.3% vs. 2.6%, $P = .0001$) [57].

In women, there is evidence of QTc variability during the menstrual cycle and pregnancy. During pregnancy, there are higher estradiol levels and the QTc gets shorter. Concomitantly, there are data showing that the occurrence of tachyarrhythmia in LQT2 patients during pregnancy is lower than for nonpregnant patients; estradiol likely has a protective effect against the occurrence of Tdp [39]. One hypothesis is that estradiol results in enhanced outward K+ current via IKr. In a comprehensive study that measured the sex hormone levels and QTc in 11 women during clomiphene stimulation for infertility, estradiol levels were seen to increase. Three of the subjects were LQT2 patients, and three of their relatives who were gene negative for LQT2 were included in the study. During their menstrual cycles, cellular and molecular analysis was done showing that high estradiol levels correlated with shorted QTc due to unenhanced KCNH2 channels. The underlying mechanism was derived based on inhibition of heat shock protein-90 (HSP90) via geldanamycin that resulted in a decrease in KCNH2 activation from estradiol. Since geldanamycin has no direct effect on KCNH2 or expression of estradiol, the conclusion was drawn that estradiol enhances interaction of HSP90 with KCNH2 channel subunits leading to an increase in ion-channel trafficking via Ikr and shortening of AP phase 3 of myocardial cells [58].

Testosterone causes a shorter QT interval in males [44]. A study that compared male groups based on total and free testosterone levels showed the average QT interval in the group with the highest quartile of testosterone levels was shorter when compared to the group with lowest testosterone levels, which had the longest average QT interval [24]. The hormonal role in ECG pattern differences between males and females is also supported by the lack of significant differences in ventricular repolarization duration among both sexes below the age of 16 years [25]. This prepubertal absence of QTc difference is explained by lack of sex hormone differences at this age. This association is also supported by the molecular analysis of testosterone effects on cardiac repolarization currents from isolated guinea pig ventricular myocytes of both males and female. Sex hormones diffuse into the target myocardial cell and activate a cytosol-specific receptor that dimerizes and binds to hormone response elements (HREs) of gene promoters in the cell nucleus, resulting in target gene transcription. It is also suggested that the gene coding for L-type calcium channels, CACNA1C, contains an HRE, and testosterone stimulates this gene expression in male rats. Furthermore, orchiectomy in rats resulted in substantial decrease in mRNA levels of subunits of the L-type calcium channels [59]. Men have a shorter J-to-T peak, which is most likely explained by the reduced concentration of L-type calcium channels due to testosterone's effect, which results in a shorter plateau phase of the AP [60,61].

The clinical importance of sex-based differences in ventricular repolarization relates to the higher rate of SCD due to ventricular arrhythmias resulting from abnormal ventricular repolarization (TdP, and VF) in women [62–66]. Acquired LQTS is due to block of IKr channels via many AADs and noncardiac drugs. Approximately 65%–75% of all drug-induced LQTSs occur in women [62,67]. When comparing the change in QTc with the AAD quinidine, ibutilide, and sotalol, small studies have shown no clear evidence that the drugs have differential effect based on sex. However, the baseline QTc is more prolonged in females relative to males. Additionally, the higher risk of TdP in women may be related to higher serum drug concentration due to relatively smaller body size in comparison to men. The studies that show a significant difference in QTc prolongation from AAD did not adjust for this difference. The sex and age differences in the QTc can be explained by longer J-to-T peak interval in women, despite women having a shorter QRS duration [60,61].

The congenital LQTS results from genetic mutations in ion channels and cellular structural proteins, with more than 12 different genes currently identified. However, two-thirds of all LQTS cases are due to three genetic mutations [68]. LQT1 and 2 are due to mutation of KCNQ1 and KCNH2, respectively, that lead to loss of function of the voltage-gated potassium channels IKs and IKr, respectively. LQT3 is associated with mutation of SCN5A causing gain of function of Na channels. These disparate changes result in prolongation of depolarization [69]. Of note, another study of LQTS patients (479 probands, 70% female, and 1041 affected family members) showed that cardiac event (syncope, nonfatal cardiac arrest, or sudden death) rates among probands and symptomatic family members were significantly different between the sexes. In males, the risk of a first cardiac event was higher by age 15 when compared to females, including both probands and symptomatic family members, while in females, events were higher between ages 15 and 40 years. These findings remained after adjustment for QTc duration [70].

Summary

Electrocardiographic sex differences are prominent and important to recognize. Disease definitions and manifestations differ between the sexes and can have significant ramifications for risk assessment. Sinus rate is generally higher in women than in men. Prolonged QTc interval is defined as >450 ms in males and >460 ms in females. In clinical practice, an ECG with QTc >480 ms in females and >470 ms in males warrants further investigation for the diagnosis of LQTS. ER pattern is defined as JPE, sharp positive deflection, or notch immediately following a positive QRS complex at the onset of the ST segment, ≥ 0.1 mV in two adjacent leads, and is a more common finding in healthy males. LQTS, BRS, and ERS all can lead to sudden death, and their very diagnosis rests on the accurate assessment of sex-specific ECG parameters.

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Part IV

Cardiac autonomic regulation

Chapter 14

Baseline autonomic characteristics

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Brief historical prospective

The word "sympathetic" dates back to Galen, a Greek physician who lived in the 2nd century. He considered nerves as conduits through which a "spirit" reach the organs, so that they could harmoniously function in concert ("sympathy") with one another. Galen's thoughts guided medical science for centuries, so that until the 18th century, the knowledge on the physiology and functioning of the autonomic nervous system (ANS) was still in an embryonic phase [1].

Nevertheless, the end of the 19th century and the beginning of the 20th century witnessed an explosion of discoveries.

In 1836, Astley Paston Cooper (1768−1841), an English surgeon and anatomist, reported that occlusion of the common carotid arteries increases blood pressure and heart rate [2].

In 1851, Claude Bernard (1813−78) reported that cutting the cervical spinal cord produced an immediate, marked drop in blood pressure, giving evidence that the brain regulates the overall cardiovascular "tone." He suggested that the sympathetic system induces its effects indirectly through actions on smooth muscles within the blood vessels, thus laying a foundation for the ideas of vasomotor system. In addition, his scripts on the philosophy of science made him one of the most important scientists of the 19th century [3].

In 1894, George Oliver (1841−1915) and Edward Albert Sharpey-Schafer (1850−1935) injecting suprarenal gland extract into a dog vein found that it greatly increased blood pressure. They also reported that there was a decrease in the caliber of the arteries and an increase of pulse tension. This was the first evidence of the body's ability to produce substances (later called hormones) capable of acting on another organ. They coined the term "endocrine" as the generic term for such secretions [4].

The dissemination of these findings immediately prompted research to isolate the active principle of the adrenal extract in a pure form.

Jokichi Takamine (1854−1922) and John Jacob Abel (1857−1938), working independently (in New York and Baltimore, respectively) identified the active principle of the adrenal gland extract. Abel called it "epinephrine," while Takamine named it "adrenaline." Abel obtained a crystalline product that appeared to be the blood pressure−increasing substance of Oliver and Schafer's extract, in 1897. While, in 1901, Takamine published the results of his own research and patented (becoming very rich) a formula slightly different from the one of Abel. Abel always declined to get involved publicly in disputes, but privately he expressed the view that he had isolated the hormone in its active form, even though his epinephrine still retained a chemical radical that he was unable to remove. Takamine had actually isolated the hormone; although, several years later, it was shown that the natural product is itself a mixture of two substances, epinephrine and norepinephrine [5].

In the meantime, at Cambridge University, John Newport Langley (1852−1925) was studying the anatomical path of the ANS and its function on different organs. In 1898, Langley coined the term "autonomous nervous system" referring to networks of nerves that derived from a group of nerve cells (ganglia) placed outside the central nervous system, which influence the body functions with a degree of independence from the central nervous system. He also identified three components of the ANS: the sympathetic, the parasympathetic (another term invented by him), and the enteric system. He described that sympathetic nerves originate from the thoracolumbar spinal cord and parasympathetic nerves from the brain stem and sacral spinal cord, whereas the enteric originates into the walls of the gastrointestinal tract. He also coined the terms "preganglionic neuron" and "postganglionic neuron"

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to define fibers placed pre- and postganglia. He defined the sympathetic and parasympathetic division based on the opposing actions that these two sets of nerves had on many organs. He also found that extracts of the adrenal gland elicited responses that were similar to those induced by sympathetic nerve stimulation. Finally, he introduced the concept of receptors and sequence of events. For all the abovementioned findings, and others, Langley is considered the father of the ANS [1,6–8]. However, also Thomas Renton Elliot (1877–1961), a young graduate student who worked in the laboratory directed by Langley for a brief period, deserves credit. Elliot performed only a few studies, but he was able to conduct a broad analysis of the comparative effects of the medullary extracts epinephrine and sympathetic nerve stimulation, and introduced the concept of chemical transmission affirming that "adrenalin might then be the chemical stimulant liberated on each occasion when the impulse arrives at the periphery" (Elliott, 1904) [7–9].

In 1907, Walter Ernest Dixon (1871–1931), a pharmacologist at Cambridge University, extending Elliott's findings, showed that even the parasympathetic nerves might transmit their effects by releasing, at their endings, a specific substance, which produce their actions [7,8].

Nevertheless, for more than a decade, whether nerves communicated with each other via a chemical or an electrical signal was a matter of debate. The definitive answer arrived from Otto Loewi.

Otto Loewi (1873–1961) demonstrated that nerve impulses are transmitted by chemical messengers. The experiment he performed to prove this is very popular. He dissected and extracted out of frogs two beating hearts: one with the vagus nerve attached and the other heart on its own. Both hearts were bathed in a saline solution. By electrically stimulating the vagus nerve, Loewi made the first heart beat slower. Then, he took some of the liquid bathing the first heart and applied it to the second heart. The addition of the liquid to the second heart made it beat slower. Thus, he reached the obvious conclusion that a soluble chemical substance released from the vagus nerve of the first heart was responsible for inhibition of the heart rate of the second heart. Therefore, Loewi proved that an electrical signaling determines a chemical event (release of neurotransmitter from synapses) that is ultimately the effector on the target tissue. Later on, he also identified that the mediator was acetylcholine and that atropine antagonizes its activity [1,7,8].

Henry Dale (1875–1968) described the actions of acetylcholine on various organs and the cardiovascular system. He noted two type of response to acetylcholine. He called them muscarinic and nicotinic, since they mimicked the effects of muscarine (poisonous deriving from the mushroom *Amanita muscaria*) and nicotine. He also described that the blood pressure effect of adrenaline was reversed by ergotoxine into a depressor way. Dale also added what may be considered another section of the ANS: the sympathetic cholinergic component, which is involved in the thermoregulatory activity [1,7]. In addition, Dale coined the terms "parasympathomimetic" and "sympathomimetic" to describe the actions of chemical substances that mimic the effects of the stimulation of parasympathetic and sympathetic postganglionic nerves, respectively [1,6,7].

In 1936, Lowei and Dale received a Nobel Prize for their discoveries relating to chemical transmission of nerve impulses.

At the beginning of the 20th century, Walter Bradford Cannon (1871–1945) gave evidence that the sympathetic nervous system and adrenal gland act together as a functional unit in stressful or emergency situations (fight-or-flight response, described below). Living organisms survive by maintaining a complex dynamic equilibrium of the internal milieu or homeostasis (term coined by him), by the control among others of heart rate, blood vessel tone, and thermogenesis [1,6,7,10].

In 1923, Heinrich Ewald Hering (1866–1948) found that mechanical stimulation of the carotid wall, nearby the carotid bifurcation, produces a significant reduction of heart rate and blood pressure. Consequently, he found the carotid sinus and gave also evidence of the baroreceptor reflex originating from the carotid sinus [6].

Soon after that finding, Corneille Heymans (1982–68), who received the Nobel Prize for Physiology in 1938, demonstrated that information related to blood pressure and oxygen blood concentration were carried to the brain not by the blood itself, but by nerves. He accomplished this by vivisection of two dogs. The head of the first dog was connected to its body only by nerves and perfused by the blood of the second dog. The body of the first dog was kept alive due to artificial respiration. In that experimental setting, he observed that when the carotid sinus of the first dog was perfused by high blood pressure (generated by blood flow of the second dog), there was a reflex relaxation of the peripheral vessels of the first dog and a decrease of its heart rate. Therefore, he demonstrated that the propagation of the two reflexes (vasodilation and bradycardia in response of high blood pressure) had occurred through the nerves and not the blood flow. Moreover, he also proposed that the carotid sinus baroreflex modifies adrenomedullary secretion reflexively [11].

In 1948, several decades after Elliot studies, Raymond Perry Ahlquist (1914–83) noted two types of responses from sympathomimetic agonists; therefore, he proposed the division of adrenoceptors into two types, α-receptors and β-receptors [12].

The identification of selective antagonists, like phentolamine and ergotamine for α-adrenoceptors (Powell CE and Slater IH, 1958), and dichloroisoprenaline and

propranolol for β-adrenoceptors (Black JW 1964, Nobel Prize 1988) gave evidence of subtypes of adrenoceptors and has marked the path of the history of many contemporary pharmaceutical treatments that have changed the prognosis of millions of patients worldwide [12].

Organization of the autonomic nervous system

The ANS consists of three components: (1) sympathetic (noradrenergic) nervous system; (2) parasympathetic (cholinergic) nervous system; and (3) enteric nervous system.

The sympathetic nervous systems and parasympathetic nervous systems have cell bodies in the brain stem and spinal cord. Autonomic nerves come from the brain stem as cranial nerves, from the thoracolumbar spinal cord as sympathetic nerves, and from sacral spinal cord as parasympathetic nerves. Autonomic nerves passing through ganglia are characterized by preganglionic and postganglionic fibers. Table 14.1 shows the pathway and messengers of the sympathetic and parasympathetic ANS transmission.

The enteric nervous system lies within the wall of the gastrointestinal tract and consists of a network of neurons that governs the function of the gastrointestinal system. It acts independently of the sympathetic and parasympathetic nervous systems, although it may be influenced by them. The enteric nervous system recently was labeled the second brain [1,7,11,13,14].

The efferent nervous activity of the ANS is largely regulated by autonomic reflexes. In many of these reflexes, sensory information is transmitted to homeostatic control centers, in particular, those located in the hypothalamus and brain stem.

The sympathetic nervous system

The preganglionic fibers are short; they come from nuclei within the brain stem that leave the central nervous system at the thoracolumbar spinal cord (T1−L3) and travel to a ganglion (often paravertebral). From there, long postganglionic neurons extend across most of the body.

At the synapses within the ganglia, preganglionic neurons release acetylcholine acting on nicotinic receptors. In response to this stimulus, the postganglionic neurons may release norepinephrine (sympathetic noradrenergic component), acetylcholine (sympathetic cholinergic component), or adrenaline (sympathetic adrenergic component), which cause the effects related with the sympathetic stimulation, activating receptors that are present on the target tissues [11−15].

Sympathetic noradrenergic stimulation triggers the constriction of peripheral blood vessels, especially of arterioles, which are the main determinant of peripheral resistance. In addition, stimulation of the sympathetic noradrenergic component determines pupils' dilatation,

TABLE 14.1 Organization of the autonomic nervous system.

	Sympathetic nervous system				Parasympathetic nervous system
Leaving the CNS from	T1−L3 of spinal cord				Brain stem and S2−S4 of spinal cord
Preganglionic nerves	Short and nonmyelinated				Long and myelinated
Preganglionic transmitter	ACh				ACh
Preganglionic receptor	Nicotinic				Nicotinic
Location of ganglia	Paravertebral				Nearby or embed the target organs
Postganglionic nerves	Short and nonmyelinated				Short and nonmyelinated
Postganglionic transmitter	Norepinephrine				ACh
Postganglionic receptor	α1	α2	β1	β2	Muscarinic
Receptors location in CVS					
Sinus atrial node			++		+++
Atrioventricular node			++		++
Atria			++		+++
Ventricles			+++		+
Arteries	+++	++	+	++	+
Vein		+		++	+

Ach, acetylcholine; *CNS*, central nervous system, *CVS*, cardiovascular system.

salivary glands secretion, heart beat increase, smooth muscle cells of the airways relaxation, and tubular reabsorption of sodium in the kidneys.

The sympathetic cholinergic component mediates thermoregulatory sweating. The neurotransmitter of the sympathetic cholinergic component is acetylcholine, which stimulates secretion from sweat glands via muscarinic receptors. Besides, sweat glands also have adrenoceptors, which evoke sweating when occupied by the neurotransmitter norepinephrine or the hormone adrenaline.

Finally, the sympathetic adrenergic component, together with adrenal medullary gland constitutes the adrenomedullary hormonal system, a part of the neuroendocrine system. Its primary activity is controlling the body's fight-or-flight response, which is a physiological reaction that occurs in response to a perceived harmful event. Adrenaline stimulates all types of adrenoceptors, causing an increase of the heart rate, blood pressure, and air passages into the lungs, as well as enlarged eye pupil, redistribution of blood to the muscles, and an alteration of the body's metabolism to maximize blood glucose levels in the brain. The reaction involves the cardiovascular system directly via impulses transmitted through the sympathetic nervous system and indirectly via catecholamines secreted from the adrenal medulla. The connection from the spinal cord to the adrenal medullary cells is direct by rapidly conducting myelinated fibers. The preganglionic sympathetic fibers ending in the adrenal medulla secrete acetylcholine, which activates the great secretion of epinephrine and norepinephrine into the bloodstream (and causing secretion of other hormones, i.e., cortisol) [11–15].

The parasympathetic nervous system

The parasympathetic nervous system acts like the opposite of an emergency system. Increased activity of this system is associated with "vegetative" behaviors, such as sleeping and digesting. The parasympathetic nervous system is responsible for the unconscious regulation of salivation, lacrimation, urination, digestion, and defecation (acronym SLUDD) [16].

Most of the nerves of the parasympathetic nervous system come from the brain stem and some from sacral spinal cord. Acetylcholine is the chemical messenger released from both the preganglionic and the postganglionic parasympathetic fibers. Ganglia of parasympathetic nervous system are located nearby the target organs. Acetylcholine binds to nicotinic receptors on the cell bodies of the postganglionic nerves, whereas receptors in the target organs are muscarinic.

Stimulation of the vagus nerve increases smooth muscle tone and secretion of stomach acid and digestive hormones. Vagal stimulation also decreases heart rate and the force of cardiac contraction.

Most of parasympathetic nervous fibers are afferents. Therefore, they carry information to the brain, such as those from baroreceptors in the wall of the carotid artery and the aorta.

In the lower part of the parasympathetic nervous system are nerves from the bottom level of the spinal cord, the sacral spinal cord. These nerves travel to the lower gastrointestinal tract, urinary bladder, and genital organs [1,7,11,14–16].

ANS and cardiovascular system

The sympathetic and parasympathetic nervous systems exert antagonistic effects on the cardiovascular system. Both components are continuously active, so that at any time, the cardiac activities and vascular tone are the net balance of the continuous interaction of these two components, which increase their activity in opposite conditions [15].

The sympathetic system governs energy needs of the body; its activity is evoked every time the request for oxygen increases, from physical activity to pathological conditions, and in case of stressful events or emergency. The sympathetic stimulation mainly evokes the constriction of blood vessels (with consequent increase in blood pressure) and the increase in heart rate and myocardial contractility.

Conversely, the parasympathetic system is most active under restful conditions, and it counteracts the sympathetic system after a stressful event for restoring the body to a restful state. Parasympathetic stimulation decreases the heart rate and causes blood vessel dilation. However, it should be noted that many blood vessels do not have parasympathetic innervations; therefore, their diameter is regulated only by sympathetic input; it is a decrease in the sympathetic tone that allows vasodilation [15].

Sympathetic component

Cardiac sympathetic preganglionic fibers, typically all myelinated, emerge from the upper thoracic segments of the spinal cord (T1–T4). After traveling a short distance, they enter the sympathetic ganglia, located at the side of the vertebral column (i.e., paravertebral ganglia), from where long postganglionic fibers depart to reach the heart and blood vessels.

Therefore, the efferent pathway of the sympathetic nervous system is the following. An electrical signal leaves the central nervous system at the spinal cord and runs fast through myelinated preganglion fibers to the paravertebral ganglia, determining the secretion of acetylcholine, at the synapse level. Then, from the ganglia, an electrical signal through the postganglionic fibers reaches the target tissues

of the cardiovascular system (heart and vessels), where it causes the final release of catecholamines (norepinephrine or adrenaline). The specific effect of the sympathetic stimulation depends upon the chemical interaction between the transmitter and the receptors present on the target tissues. Into a target tissue, the neurotransmitter may meet different types of receptors characterized by the capability of generating specific actions; for example, in the vascular smooth muscle cells, there are α-receptors that evoke vasoconstrictions, while β-receptors evoke vasodilation (Table 14.2).

The net response to agonists that, like adrenaline, stimulate both types of receptors depends upon the relative importance of each receptor population [1,7,11–17].

α- and β-adrenergic receptors

In the cardiovascular system, there are α1-, α2-, β1-, and β2-adrenergic receptors (also divided in subtypes based on the differential affinity for chemical substances) [12].

In the cardiovascular system, α1- and α2-receptors are mainly in smooth muscle cell of vessel wall [12]. Their activation by norepinephrine causes vasoconstriction. Norepinephrine also is an agonist at β1-adrenoceptors, but, unlike adrenaline (which stimulates all type of adrenoceptors), norepinephrine is a relatively poor agonist at β2-receptors [12].

The concentration of adrenoceptors in the blood vessels varies from vascular bed to vascular bed, and the vascular tone results from the simultaneous activation of receptors that are differentially influenced in the different vascular areas by the transmitters coming out from the sympathetic nerve endings. The receptors, the activation of which more importantly contributes to the basal vascular tone, are those that are "innervated": the α1-adrenoceptors in the arterial vessels, the α1- and β1-adrenoceptors in the heart, and α2- and β2-adrenoceptors in the veins [12].

In the cardiovascular system, the β1-receptors are mainly in the sinus atrial node, in atrioventricular node, and in both on atrial and ventricular myocytes. The activation of β1-receptors increases heart rate (via the sinus atrial node and atrioventricular node conduction) and myocardial contractility (as result of increased intracellular calcium concentrations) [12].

The β2-adrenergic receptors are in a smooth muscle cell of peripheral and coronary circulation. Their activation causes vasodilatation, which, in turn, increases blood perfusion especially in the heart and skeletal muscle. However, because these receptors seem not to be innervated, they are primarily activated by circulating catecholamine [12–18].

Sympathoadrenal system

Some preganglionic fibers of the sympathetic nervous system end directly in the adrenal medulla. These fibers stimulate the secretion of adrenaline from the adrenal medulla gland, and therefore they are strictly involved in the fight-or-flight response. Additionally, activation of this receptor also induces renin release, which contributes to the final blood pressure, as well as plasma sodium levels and blood volume. There is evidence that neurohormonal regulation plays a critical role in the pathogenesis and progression of several cardiovascular diseases [19]. Plasma and tissue levels of noradrenaline, adrenaline, angiotensin II, aldosterone, and other mediators are increased in hypertension, heart failure, and some arrhythmias. Their activities correlate with the severity of disease. Therefore, opposing the effect of elevated adrenergic and/or angiotensin, renin–angiotensin–aldosterone signaling is the main objective of several treatment strategies [20–23].

TABLE 14.2 Neurotransmitters and receptors acting on the cardiovascular system.

Autonomic nervous System Component	Neurotransmitters	Receptor	Target tissue				
			Vessels		Heart		
			Constriction	Dilation	Inotropy	Chronotropy	Dromotropy
Sympathetic	NE	α1	↑↑↑		↑	↑	↑
	NE	α2	↑				
	NE	β1	↑		↑	↑	↑
	Adrenalin	β2		↑	↑	↑	↑
Parasympathetic	ACh	M2		↑	↓	↓	↓

Ach, acetylcholine; *M*, muscarinic; *NE*, norepinephrine; *PNS*, parasympathetic nervous system; *SNS*, sympathetic nervous system; ↑, increase; ↓, decrease.

Parasympathetic component

The parasympathetic nervous system plays an antagonistic role in regulating heart function, with respect to the sympathetic system [24]. Vagal stimulation decreases the heart rate and the force of cardiac contraction. This happens by two mechanisms: firstly, directly, through preganglionic fibers that reach the parasympathetic ganglia placed into the myocardium and the vagal stimulation inhibits contraction of myocardial cells and secondly, indirectly by occupying acetylcholine receptors of sympathetic noradrenergic nerves in the myocardium [24–26].

The parasympathetic innervation originates predominantly in the nucleus ambiguus of the medulla oblongata. The efferent parasympathetic nerve fibers are carried to the heart almost entirely by the vagus (10th cranial) nerves. The pre- and postganglionic vagal fibers synapse in ganglia that lie on the epicardial surface or within the cardiac tissue. Most of the vagal nerve fibers converge into a distinct fat pad located between the superior vena cava and the aorta on the pathway toward the sinus and atrioventricular nodes [27]. The vagal ganglia in different fat pads control different regions of the heart.

The distribution of the vagal innervation varies from region to region. The sinoatrial and atrioventricular nodes and the atria are more richly innervated by vagal fibers than are the ventricles and coronary vessels [24,25]. In addition, preganglionic fibers that travel in the right and left vagus nerves are distributed asymmetrically to the various structures in the heart. The right vagus nerve has somewhat greater influence on the sinoatrial node than does the left vagus nerve, whereas the left vagus nerve has greater effect on the atrioventricular conduction system. In fact, right vagus nerve stimulation tends to produce more sinus bradycardia, whereas the left vagus nerve stimulation tends to produce more atrioventricular nodal block [28,29].

The predominant neurotransmitter of the pre- and postganglionic vagus nerve terminals is acetylcholine. The main type of cholinergic receptor on the postganglionic neuron is nicotinic. The main type of cholinergic receptor on the membrane of cardiac effector cells is muscarinic. Therefore, nicotine-blocking agents (such as hexamethonium) and muscarinic-blocking agents (such as atropine) can suppress parasympathetic transmission from the pre- to postganglionic neuron and from postganglionic fibers to the cardiac effector cells, respectively [24–26].

In addition, there is evidence that there are also other neuropeptides, like vasoactive intestinal polypeptide (released along with acetylcholine from postganglionic fibers), which serve to modulate the effects of the acetylcholine and may affect the cardiac tissue [24,30].

ANS on the sinus and atrioventricular node

The sinus node is richly innervated with postganglionic adrenergic and cholinergic fibers, although it is predominantly under parasympathetic control. The greatest concentration of vagal fibers in the heart is in the sinus node [31–34]. The sympathetic effects are mediated primarily through stimulation of β-receptors [31–34]. Tonic stimulation of the vagus nerves prolongs the cardiac cycle length. However, over several stimulation frequency ranges, the chronotropic response acts paradoxically, and the cardiac cycle length decreases as the frequency of stimulation rises [35].

The principal influence of vagal activity on atrioventricular nodal conducting fibers is to hyperpolarize the cell membrane and to reduce the action potential upstroke velocity [36–38]. Therefore, vagal activity diminishes the velocity of impulse propagation through the atrioventricular node and prolongs the refractory period of atrioventricular node fibers [24,36–38]. The clinical consequences are, on one side, that intense vagal activity may induce even second- or third-degree atrioventricular block and, on the other side, that increasing vagal activity may interrupt episodes of reentrant tachycardia that include the atrioventricular node in the reentry loop.

ANS on the atrial and ventricular tissue

Vagal influences on the atrium predominate over sympathetic actions. Vagal activity profoundly inhibits atrial contraction [24,25,39–43], and thus, it may attenuate the atrial contribution to ventricular filling [44]. There is evidence that even a single vagus stimulus can diminish atrial contraction by more than 50%, and 2 or 3 stimuli in rapid succession can reduce contraction by almost 100% [41]. Because of nonhomogeneous vagal innervation to the atrium [45,46], intense vagal stimulation can produce dispersion of atrial refractoriness and, consequently, induction of atrial fibrillation [47,48].

Ventricles have considerable sympathetic innervation. The left ventricle is predominantly innervated by the left-sided sympathetic fibers. The vagus nerves innervate also heart ventricles [24,25]. Its stimulation significantly reduces ventricular contractility. The first evidence came only in 1965, from studies conducted on dogs placed on total heart bypass, so that there was total control of heart rate, preload, afterload, coronary perfusion pressure, oxygen partial pressure, and other variables that could have influenced the interpretation of the response to vagal stimulation [49]. When the heart beats spontaneously,

the changes in ventricle contractility paralleled the changes in heart rate, whereas when the heart rate was artificially kept constant, the reduction in ventricular contractility related directly to the frequencies of vagal stimulation [49]. Vagal stimulation shifts ventricular function in the directions that denote depressed contractility [24,25].

There are data consistent with a different distribution of sympathetic and vagal fibers in the ventricular wall [50]. Specifically, sympathetic nerves traverse the ventricle in the subepicardium, sending branches deeply to the subendocardium. On the contrary, vagal nerves soon after the atrioventricular groove penetrate from the subepicardium into the ventricular wall, from there dividing into several minor branches. Differences in innervation patterns between sympathetic and parasympathetic fibers are important in understanding mechanisms of arrhythmias following myocardial infarction [51–53]. Transmural myocardial infarction interrupts sympathetic innervation [28,51–53]. Studies in humans have suggested that vagal activity is reduced and sympathetic activity is enhanced following myocardial infarction and that this altered autonomic balance may in part modulate the incidence of sudden death and poor outcome following acute myocardial infarction [54–58]. The different spatial distribution may probably account also for the difference in the sympathovagal balance between patients with spontaneous versus balloon-induced coronary occlusion; the former being characterized by increased sympathetic activity and the latter by enhanced parasympathetic activity [59].

Autonomic interaction

The vagal effect is usually not prominent in the absence of concurrent sympathetic activity, but it becomes considerable when the sympathetic system is very active [23,60,61]. The inhibitory effects of vagal activity on the heart usually do not summate in a simple algebraic fashion with the stimulatory effects of the concurrent sympathetic activity [23]. The nonlinear summations of the vagal and sympathetic responses are referred to as "autonomic interaction." Such interaction is very pronounced with respect to the regulation of certain cardiac function, whereas it is much less pronounced with respect to other cardiac functions. For example, the inhibitory effect of vagal stimulation on heart rate is higher in the presence than in the absence of tonic sympathetic stimulation [60]. In contrast to the regulation of heart rate, the autonomic interaction is much less evident in the control of atrioventricular conduction [60].

The left ventricular contractile force is diminished slightly during the infusion of acetylcholine into the coronary artery of a dog. However, infusing the same dose of acetylcholine during concurrent sympathetic nerve stimulation (or norepinephrine administration), the reduction of the ventricular contractile force was more pronounced [23]. Moreover, the increased level of sympathetic activity augmented substantially the negative inotropic effect of the vagal stimulation [60]. Qualitatively, similar sympathetic–vagal interaction has also been demonstrated in the atrial myocardium [62].

Paradoxical effect of vagal stimulation

Under certain experimental condition, vagal stimulation induces substantial increases rather than decreases in heart rate [63–66]. There is evidence that the fast component of the vagally induced tachycardia is abolished after β-adrenergic receptor blocked, but the slow component remains. Therefore, on β-adrenergic receptor blockers, enhancing vagal activity, heart rate increases, whereas those diminishing vagal activity heart rate decrease. The dependence of the tachycardia on efferent vagal activity suggested that some other substance release from vagal nerve endings could evoke the vagally induced tachycardia. Indeed, immunohistochemical studies show that parasympathetic nerve terminals vesicles store, in addition to acetylcholine, various substances, such as adenosine triphosphate and neuropeptides like the vasoactive intestinal polypeptide [30], which causes the vagally induced tachycardia noted as early as 1936 [64,65], whereas vasoactive intestinal polypeptide antagonists attenuate vagally induced tachycardia [67].

The intrinsic cardiac ANS

In addition to the extrinsic ANS, the heart is also innervated by a complex intrinsic ANS.

Armour et al. provided a detailed map of the distribution of autonomic nerves in human heart [68]. Throughout the heart, numerous cardiac ganglia, each of which contains 200 to 1000 neurons, form synapses with the sympathetic and parasympathetic fibers that enter the pericardial space [68,69]. The vast majority of these ganglia are organized into ganglionated plexi on the surface of the atria and ventricles [68]. The intrinsic cardiac ANS is a complex network composed of ganglionated plexi, concentrated within epicardial fat pads, and the interconnecting ganglia and axons [68–72]. The ganglionated plexi may function as integration centers modulating extrinsic and intrinsic cardiac ANS activities [73].

In the atria, ganglionated plexi are concentrated in distinct locations on the chamber walls [68]. Specifically, the sinus node is primarily innervated by the right atrial ganglionated plexi, whereas the atrioventricular node is innervated by the inferior vena cava–inferior atrial ganglionated plexi (at the junction of inferior vena cava and the left atrium) [69,74,75].

Another region that is richly innervated by the ANS and has a high density of ganglionated plexi is the pulmonary

vein–left atrium junction, which contains closely located adrenergic and cholinergic nerves [76].

In the ventricular, ganglionated plexi are primarily located at the origins of several major cardiac blood vessels: surrounding the aortic root, the origins of the left and right coronary arteries, the origin of the posterior descending artery, the origin of the left obtuse marginal coronary artery, and the origin of the right acute marginal coronary artery [68,74].

Ganglionated plexi have been shown to play a significant role in different arrhythmias, including atrial fibrillation. Therefore, ganglionated plexi ablation has become an adjunctive procedure in the treatment of atrial fibrillation [77,78].

Immediately after removal of all nerve inputs to the heart, activities within the ganglionated plexi are markedly suppressed [79–81]. However, there is evidence that following chronic removal, neuronal activities within the ganglionated plexi return [82]. These data suggest that maintenance of inotropic function in the heart, even when functioning independent of CNS influences, depends not only by circulation catecholamines [83] but also on levels of activity generated by neurons within the intrinsic cardiac nervous system.

Role of sex hormones in the ANS modulation of cardiac activities

In the ANS modulation of cardiac activities, sex hormones are also involved. Receptors for estrogen, progesterone, and testosterone have been identified in brain centers assigned to the regulation of cardiovascular function [84,85]. Available data support the view that among those hormones, estrogens have the major role. Indeed, animal studies revealed that intracerebral administration of estrogen increases vagal tone and suppresses sympathetic efferent activity, whereas these actions are dampened by intracranial injection of estrogen receptor antagonists [86]. As in central nervous system, similarly, at peripheral levels, estrogen modulated the final cardiac function, suppressing sympathetic and elevating parasympathetic tone [87]. Additionally, progesterone and estrogen have a synergistic effect to increase the densities of muscarinic and β-adrenergic receptors in cardiac tissue, as well as to cause a decrease in the binding affinity of β-adrenergic receptors in vivo [88].

Sex differences in the ANS

Despite the similar concentration of plasma and urinary excretion of norepinephrine and adrenaline between males and females at rest [88], several studied using analysis of heart rate variability (HRV, which provides information on sympathovagal balance) demonstrated that males have a preponderance of sympathetic over vagal control of cardiac function [89,90].

Furthermore, some studies showed that resting sympathetic nerve activity to peripheral muscles is higher in man than women, particularly below the age of 50 years [88]. Similarly, in response to exercise, norepinephrine spillover is greater in men than women [88]. Besides, several studies have reported that men show a greater response in systolic blood pressure not only to physical activities (including treadmill walking, rowing and cycling) but also to a number of cardiovascular stressors [91,92]. Accordingly, finger blood flow is reduced in response to infused adrenergic agonists in men, but not in women, and forearm vasoconstrictor response is greater in men than women [88,93].

In response to head-up tilt, the increase in plasma norepinephrine is significantly greater in males than females, and HRV analysis demonstrated that young females, as well, produce a lower sympathetic tone than young men [94].

ANS in the different phases of the menstrual cycle

In women, the concentration of sex hormones differs between pre- and postmenopausal age, but even during the premenopausal age at diverse phases of the menstrual cycle.

Hormonal fluctuations that occur during the normal menstrual cycle may alter sympathetic outflow. Indeed, plasma concentration of norepinephrine and muscle sympathetic nerve activity were found higher in the midluteal than the early follicular phase [95], but vagal cardiac baroreflex sensitivity was not affected by change of hormones secretion during the menstrual circle [95]. However, Huikuri et al. found that middle-age women have reduced baroreflex sensitivity than men, and postmenopausal women on hormone replacement therapy (HRT) have higher baroreflex sensitivity than those not on HRT [96].

Postmenopausal women exhibited both a higher basal level of norepinephrine and a greater increase in heart rate, systolic blood pressure, and norepinephrine excretion in response to psychological stressors than premenopausal women [97–99].

The effect of ovarian hormones on vagal and sympathetic influences on the cardiovascular system was also investigated. It has been shown that an acute ovarian hormone withdrawal induced by oophorectomy causes an imbalance of the autonomic nervous control of the cardiovascular system, due to a significant reduction in the parasympathetically mediated indexes of HRV [100].

Specifically, the surgical menopause caused a decrease in cardiac vagal modulation and a shift of autonomic cardiovascular control toward sympathetic hyperactivity. But 3-month cycle of estrogen replace therapy returned HRV values to a level comparable to that recorded before oophorectomy. This observation suggests that estrogen alone is involved in sympathovagal balance in fertile women through an inhibitory mechanism of the sympathetic tone, whereas progestin or other ovarian hormones play a marginal role. However, natural hormones have a more complex role.

Healthy postmenopausal women have an increased sympathetic drive, which is significantly reduced with chronic estrogen replace therapy [101].

In conclusion, available data support the view that estrogen exerts a cardiovascular protective role by its influence on autonomic nervous function. Such influence on ANS activities both at central and peripheral levels tends to suppress sympathetic tone and promote parasympathetic activity to the cardiovascular system.

Conclusions

Between the end of the 19th century and the mid-20th century, it became clear that a part of the nervous system is responsible for physiological integrity of cells and tissues. The ANS guarantees an unconscious adaptation and functioning of the organs throughout the body, by facing with an unlimited and continuous number of stimuli for change, both from the internal and external environment. Two components of the ANS, sympathetic and parasympathetic systems, which are constantly active and have antagonist effects, control the cardiovascular tone that is finally the result from their interaction. Electrical signals leave the central nervous system from the spinal cord, run through preganglion fibers, and reach the ganglia (located paravertebral or embed to the effector tissue, for sympathetic or parasympathetic system, respectively), which determines the secretion of acetylcholine, at the synapse level. Then, from the ganglia, an electrical signal through the postganglionic fibers reaches the target tissues where the final release of neurotransmitter is caused. The specific effect of the ANS stimulation depends upon the chemical interaction between the transmitter and the receptors present on the target tissues, considering either quality or quantity. The identification of several types and subtypes of receptor had permitted the development of specific drugs with antagonist and agonist effects that had changed significantly the prognosis of millions of patients.

Moreover, quite recently, it was found that the heart has also an intrinsic nervous system that interacts with the ANS in specific regions on the pericardial surface. The ablation of the neural tissue placed in some of these areas changes the natural history of several tachyarrhythmias.

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Chapter 15

Autonomic responses to postural provocations

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Incidence of different cardiovascular pathologies and their clinical manifestations are well known to differ between females and males. In cardiac electrophysiology, this includes less frequent ventricular fibrillation [1] and more frequent torsade de pointes [2] in premenopausal females. Important studies investigated sex differences in ventricular repolarization [3–5].

Somewhat lesser attention has been paid to the sex differences in cardiac autonomic modulations although the importance of autonomic control of process involved in arrhythmogenesis is well documented [6,7]. Several noninvasive studies of heart rate variability (HRV) described increased high frequency and lowered low frequency modulations in resting females compared to males [8–10] albeit other studies failed to find these sex differences [11,12]. Little is known about sex differences in autonomic responses to provocations although the importance of these responses is well understood [13].

The sex differences in the autonomic responses to postural provocations have recently been reported in a study of a relatively large population of healthy subjects of both sexes [14]. This chapter recapitulates that study while also showing that the previously reported results are closely reproducible in other datasets.

Investigations

Investigated populations

The available data originated from two clinical pharmacology studies conducted in healthy subjects. In both studies, repeated 12-lead day-time Holter recordings were made in all study subjects while they were on no treatment. All subjects had a normal screening electrocardiogram and normal clinical investigation usual in clinical pharmacology studies [15]. The original studies were appropriately ethically approved, and all participants gave written informed consent.

Female subjects of the study had a negative pregnancy test and for the duration of the clinical pharmacology study were not on hormonal contraceptives or any other hormonal therapy. Body heights and weights of the subjects were measured at screening of the source study. Body mass index was calculated as w/h^2 where w is the body weight in kilograms and h is the body height in meters.

The analysis of the first study investigated data of 175 and 176 healthy females and males, aged 32.6 ± 9.8 and 33.5 ± 8.4 years, respectively (no statistical difference between female and male ages). The second study was smaller and analytical data were available from 18 to 22 healthy females and males, aged 31.4 ± 9.4 and 29.1 ± 6.4 years, respectively (again with no statistical difference between female and male ages).

Postural provocations

The postural provocations were slightly different in both studies.

Per protocol of the first study, drug-free recordings were obtained at four different days within a 25-day period. At each of these days, the subjects followed two different procedures of postural provocations. During the first procedure (test 1), 10-min strict supine position was followed by 10-min unsupported sitting position, followed by 15-min unsupported standing position, followed by 10-min strict supine position. During the second procedure (test 2), the standing and sitting positions were reversed, i.e., a 10-min strict supine position was followed by 15-min standing position, followed by 10-min sitting position, followed by 10-min strict supine position. Postural position changes were made actively by the study subjects with the pre-protocol instruction to achieve the new body position in no more than 20 s.

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The protocol of the smaller second study included drug-free recordings at three different days within a 28-day period. The subjects were randomized into two subpopulations of the same size. In the first subpopulation, each of the drug-free recordings contained two separate provocative procedures consisting of 10-min supine position, followed by 10-min sitting, 10-min standing, and final 10-min supine position. In the other subpopulation, each of the drug-free recordings also contained two separate provocative tests consisting of 10-min supine, followed by 10-min standing, 10-min sitting, and final 10-min supine position.

During the provocative tests of both studies, the subjects had no contact with each other, were not allowed to speak, and while in the prescribed positions were instructed to make no body movements apart from shallow breathing.

On each drug-free recording days of both studies, the provocative tests were performed in the afternoon separated by approximately 1-h gap. During these days, the subjects did not have any breakfast and consumed a light lunch approximately 4 h prior to the first postural test. They were allowed to drink water and/or zero-caloric noncaffeinated drinks between the lunch and the first test and between the tests. The subjects were not allowed to smoke at least 24 h before each of the investigation days.

Heart rate and heart rate variability data

Continuous 12-lead Holter recordings with electrodes in Mason–Likar positions were obtained during the drug-free days of both studies. Using previously described measurement procedures [16], individual QRS complexes were identified and classified as belonging to sinus rhythm or corresponding to supraventricular or ventricular ectopic beats. Series of RR intervals measured at a 1 kHz resolution were obtained with systematic timing of QRS complexes achieved by calculating their maximum cross correlations.

For the purposes of tracking heart rate changes, heart rate was measured in 10-s windows that were moved through the continuous recordings in 5-s steps.

To study the autonomic responses, 5-min intervals were obtained between 4.5 and 9.5 min of each postural position as well as between 9.5 and 14.5 min of the standing positions of the first study. This eliminated the transition periods during which the heart rate was unstable because of postural changes. In each of these nonoverlapping 5-min intervals, heart rate was obtained from the averaged RR-interval durations. Subsequently, in each of these 5-min intervals, the sequence of RR intervals was detrended and Blackman–Tukey modification of Fast Fourier transformation was used to obtain HRV spectra, providing total power, and low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.4 Hz) power components [17]. The very low frequency components were not considered in the analyses.

Since the absolute measurements of the LF and HF frequency components of HRV cannot be meaningfully compared between episodes that differ substantially in the underlying heart rate, quasi-normalized $nLF = LF/(LF + HF)$ and $nHF = HF/(LF + HF)$ components were obtained. For each analyzed interval, $nLF + nHF = 1$. Therefore, for data evaluation, only nHF measurements were used.

Data presentation

Continuous data are presented as mean ± standard deviation. Because of the sizes of the populations, statistical evaluation concentrated primarily on the data of the first study. The second study was used for confirmation purposes. Where appropriate, graphic displays show data means with dual-sided 95% confidence intervals derived assuming normal distribution. Corresponding measurements in females and males were compared using standard t-tests assuming different standard deviations. Cumulative density distributions were compared by Kolmogorov–Smirnov tests. Dependencies of electrocardiographic measurements on age and on underlying heart rate were studied by means of linear regressions calculated together with 95% confidence interval bands. The slopes of the linear regressions between females and males were compared. *P*-values below 0.05 were assumed statistically significant.

Observations

Heart rate

Fig. 15.1 shows the development of heart rates during test 1 and test 2 in females and males of the first study. Although, as expected, females had a slightly higher resting heart rate at the beginning of the tests, the intraindividual heart rate response was similar in both sex groups (Fig. 15.2). During both tests, the heart rate increases from initial supine to the terminal part of the standing period were somewhat unexpectedly large and reached, on average, approximately 30 beats per minute (bpm) in both sex groups.

In the second smaller study, heart rate changes were investigated in the first and second recordings of each drug-free day separately. Fig. 15.3 shows these comparisons in females (8 and 10 females were randomized into the subpopulations of the first and second type of postural tests, respectively). The same results for males are shown in Fig. 15.4 (12 and 10 males were randomized into the subpopulations of the first and second type of postural tests, respectively). Although the graphs in Figs. 15.3 and 15.4 show less smooth profiles compared to those in Fig. 15.2,

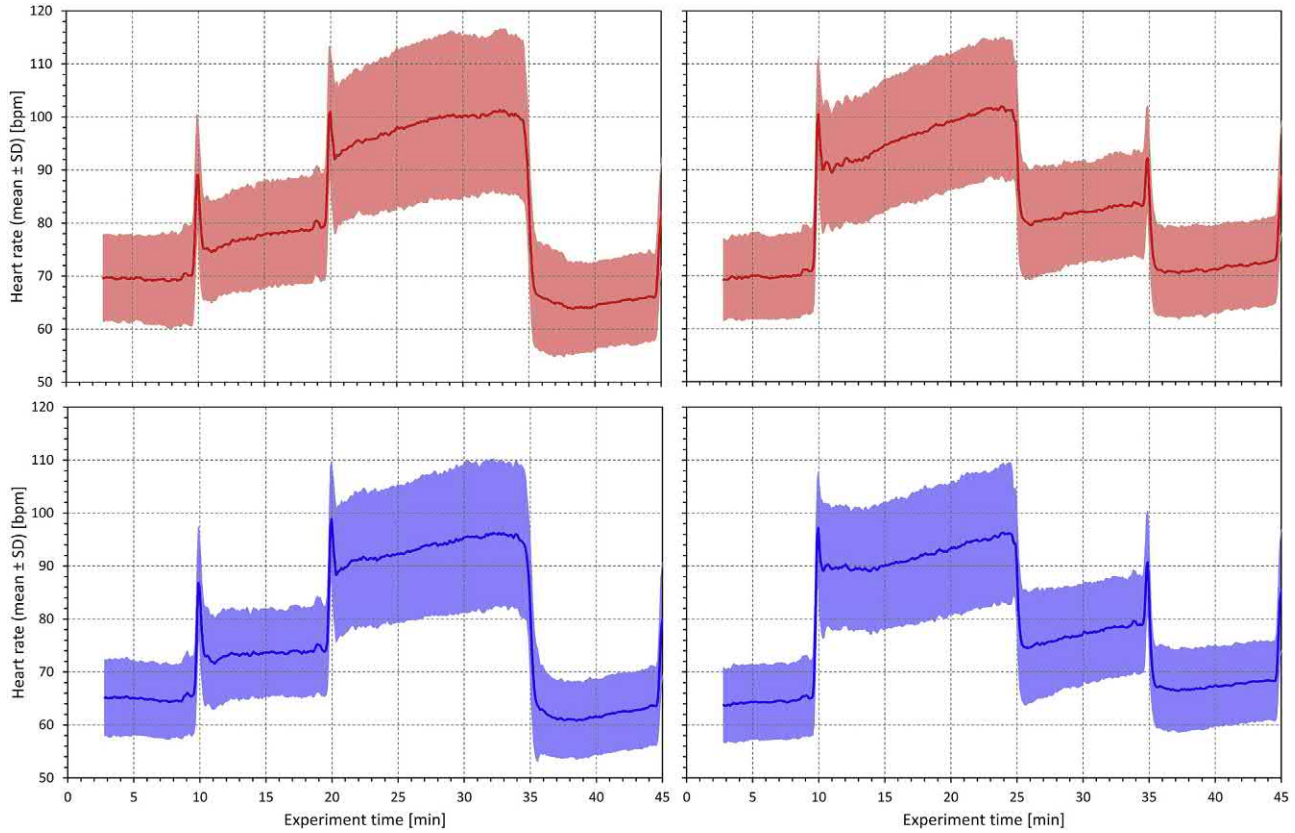

FIGURE 15.1 Population heart rates during the postural tests of the first study with visible changes during individual test phases. The panels on the left correspond to the postural test 1, the panels on the right to the postural test 2. The top panels show the heart rates measured in females (in red), the bottom panels the heart rates measured males (in blue). The *bold lines* show the mean heart rates, while the *colored areas* show the bands of ± standard deviation of heart rates. *Partly reproduced with permission from Hnatkova K, Šišáková M, Smetana P, Toman O, Huster KM, Novotný T, Schmidt G, Malik M. Sex differences in heart rate responses to postural provocations. Int J Cardiol. 2019. https://doi/10.1016/j.ijcard.2019.09.044.*

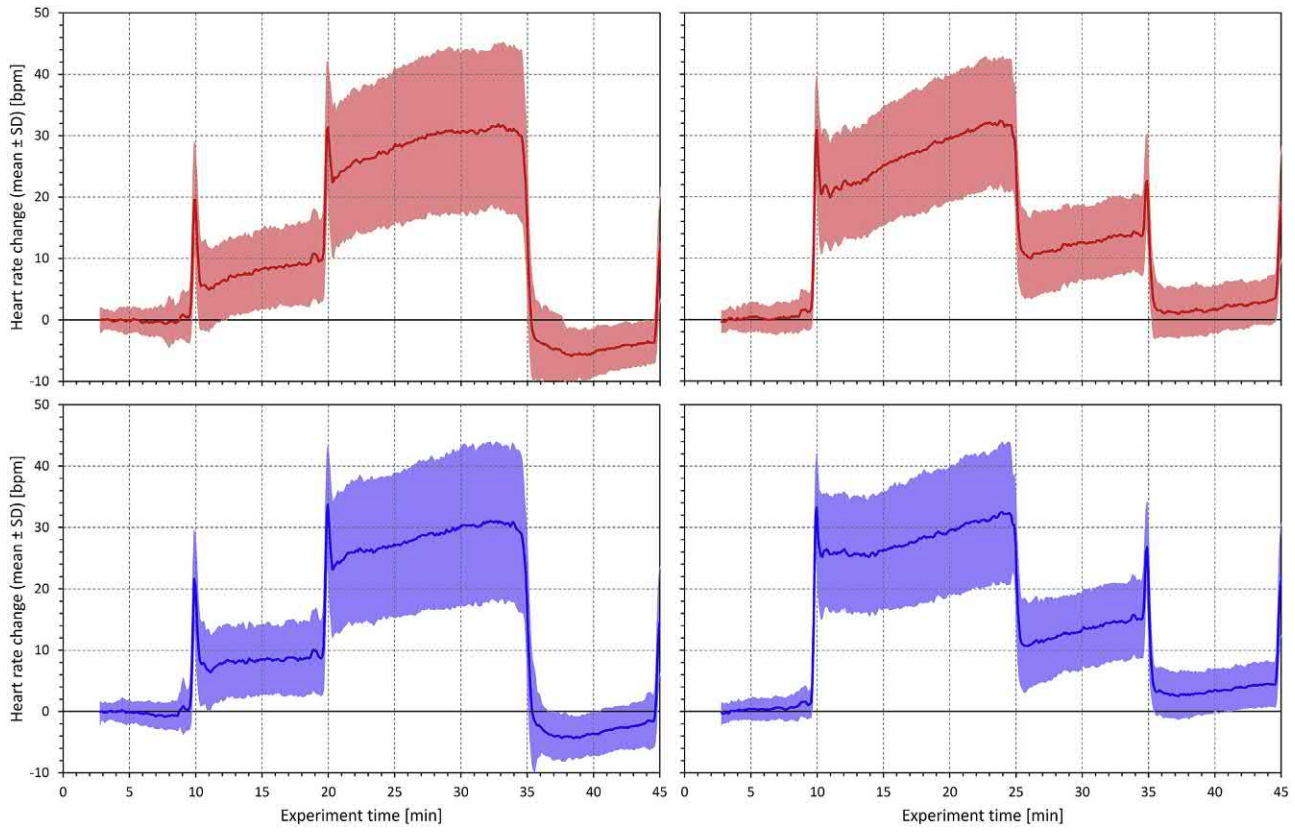

FIGURE 15.2 Population heart rate changes during the postural tests of the first study (compare with Fig. 15.1). The panels on the left correspond to the postural test 1, the panels on the right to the postural test 2. The top panels show the intrasubject heart rate changes measured in females (in red), the bottom panels the intrasubject heart rate changes measured in males (in blue). The *bold lines* show the mean heart rate changes, while the *colored areas* show the bands of ± standard deviation of heart rate changes. *Partly reproduced with permission from Hnatkova K, Šišáková M, Smetana P, Toman O, Huster KM, Novotný T, Schmidt G, Malik M. Sex differences in heart rate responses to postural provocations. Int J Cardiol. 2019. https://doi.org/10.1016/j.ijcard.2019.09.044.*

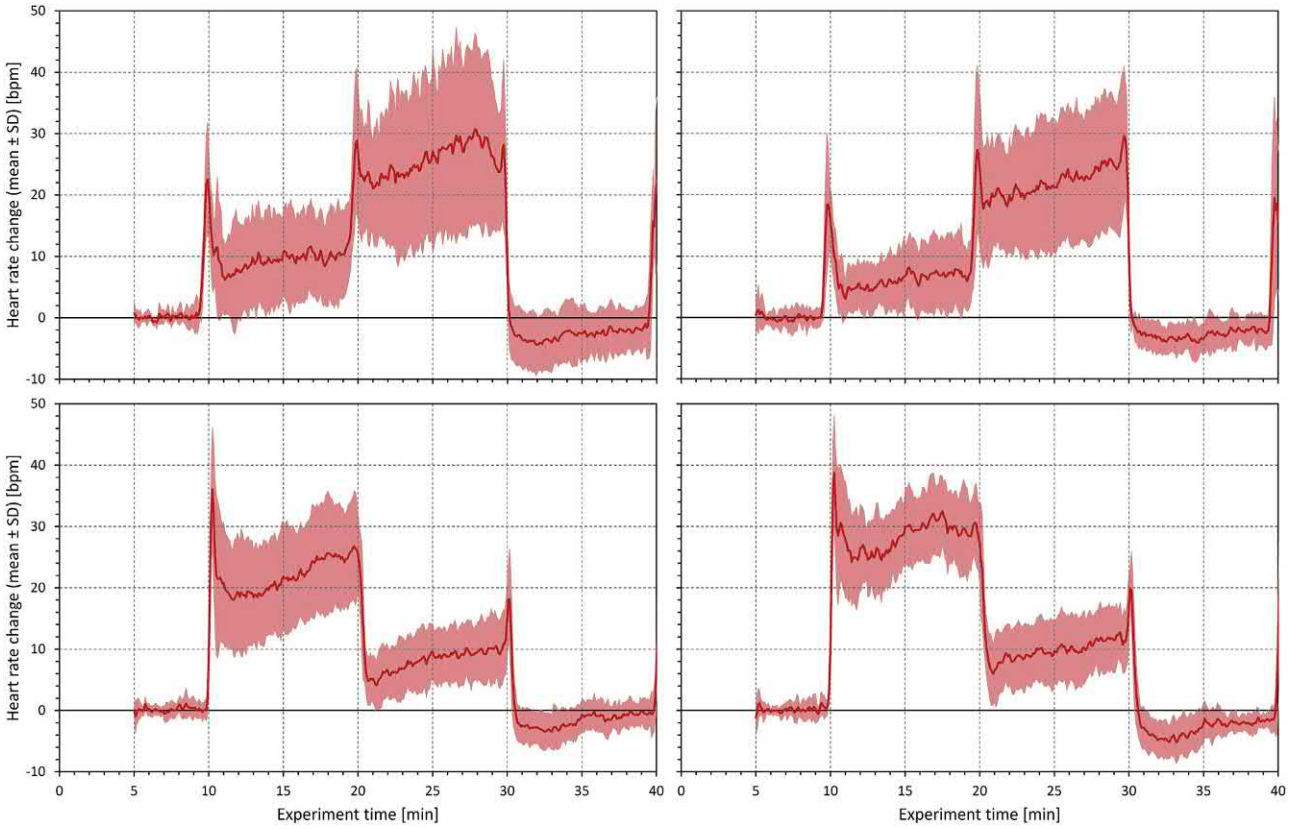

FIGURE 15.3 Intrasubject heart rate changes during the postural test in females of the second study. The top part of the figure shows the heart rate changes during the supine → sitting → standing → supine test, the bottom part of the figure shows the heart rate changes during the supine → -standing → sitting → supine test. The panels of the left show the rate changes during the first tests of the baseline days, the panels on the right the rate changes during the repeated second tests during the baseline days. The *bold lines* show the mean heart rate changes, while the *colored areas* show the bands of ± standard deviation of heart rate changes. Note the reproducibility of the results and compare with the top panels of Fig. 15.2.

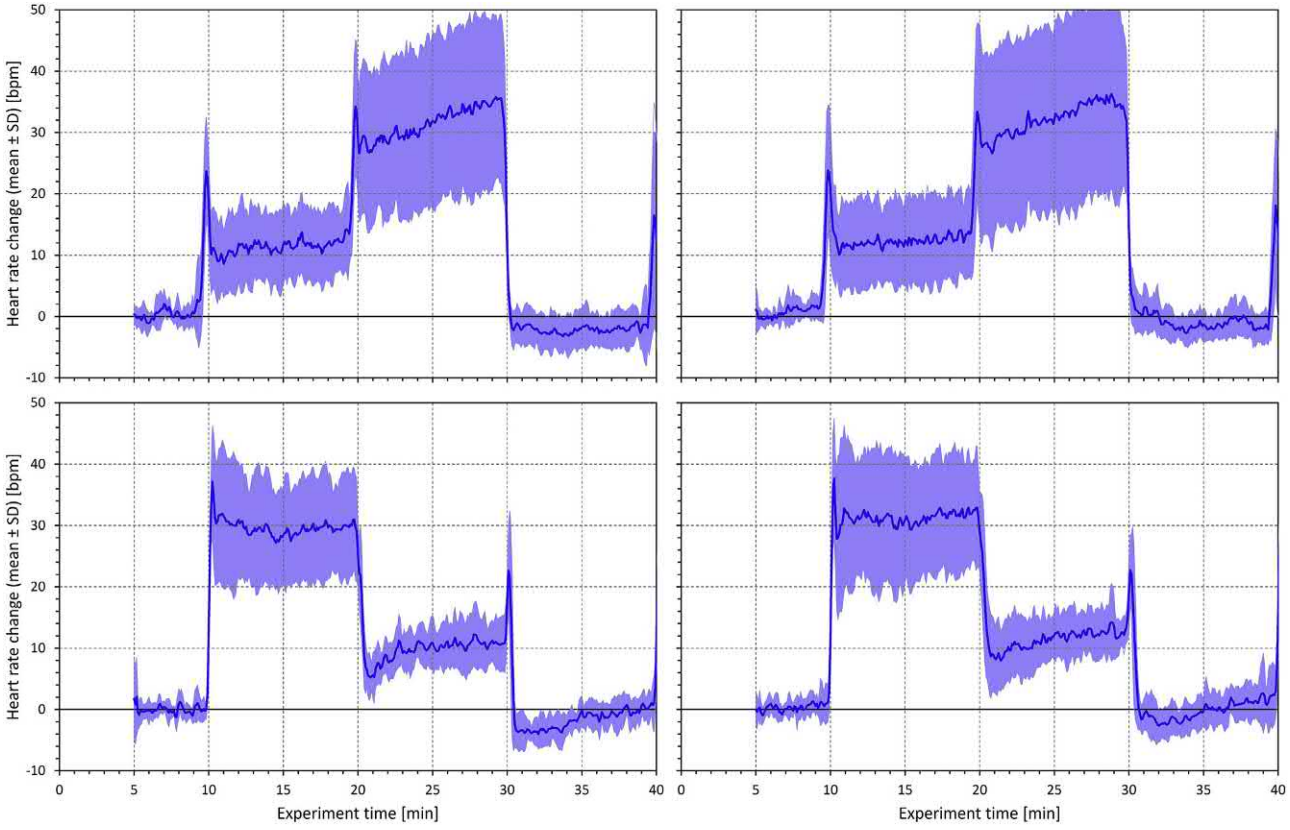

FIGURE 15.4 Intrasubject heart rate changes during the postural test in males of the second study. The top part of the figure shows the heart rate changes during the supine → sitting → standing → supine test, the bottom part of the figure shows the heart rate changes during the supine → -standing → sitting → supine test. The panels of the left show the rate changes during the first tests of the baseline days, the panels on the right the rate changes during the repeated second tests during the baseline days. The *bold lines* show the mean heart rate changes, while the *colored areas* show the bands of ± standard deviation of heart rate changes. Note the reproducibility of the results and compare with the bottom panels of Fig. 15.2.

this was caused purely by the smaller size of the population. In this second study, heart rate increases in males were visibly larger than in females but, in principle, the results agreed well between the two studies.

Heart rate and heart rate variability changes

Heart rate and HRV data in prespecified 5-min intervals of study 1 are summarized in Table 15.1. The results of study 2 were equivalent albeit with larger variability due to smaller population sizes.

For the first study, Fig. 15.5 shows these data graphically for heart rate and nHF values. It demonstrates that while the heart rate reaction was similar in both sex groups (albeit starting from a different baseline level), the nHF reaction was very different in females and males. Consistent with previous reports [8,9], females showed larger nHF values at supine baseline. Nevertheless, the reduction of nHF by standing was more pronounced in females and during standing periods, the sex groups showed either little (during the middle 5-min period of standing at test 2) or no statistically significant difference in nHF (during all other standing 5-min periods).

Fig. 15.6 shows equivalent results for the second study. In this investigation, the sex differences were even more marked. Although females of the second study responded to the postural provocations with lesser heart rate increases compared to those seen in males, their changes of the nHF values were again larger than those in males with the sex differences in nHF profiles exceeding those seen in the first study.

The sex difference in nHF reaction is shown graphically by the cumulative distributions presented in Fig. 15.7. The figure summarizes data of the first study since the second study was too small for similar distribution comparisons. While the intraindividual supine → sitting → standing changes in heart rate show similar distribution shift in females and males, the corresponding distribution shifts in nHF are substantially different, especially concerning the sitting → standing changes.

This was further confirmed by the cumulative distribution of intraindividual heart rate and nHF changes from 5-min windows of initial supine positions to the standing position (intraindividual averages of both tests of the first study) which are shown in Fig. 15.8. While there was no statistically significant difference between the distribution of the heart rate differences in females and males, the decrease in nHF was not statistically different between the sexes for the position change from supine to sitting but it was significantly larger in females compared to males for the change from sitting to standing ($P < .001$) and consequently also for the change from supine to standing ($P = .001$).

Covariates

As with the cumulative distributions, covariates of the observations were investigated in the first study. As expected, both intraindividual heart rate and nHF changes during postural changes showed relationship to age (Fig. 15.9). Supine → standing heart rate change became lower with advancing age in both females ($P < .001$ in both tests) and in males ($P = .026$ and $P = .021$ in test 1 and test 2, respectively). Although the figure shows that the slopes in females were steeper than in males, the difference was not statistically significant.

The intraindividual nHF changes were also related to age ($P < .001$ in all comparisons). Contrary to the heart rate changes, the slopes were significantly steeper in females compared to males ($P = .002$ and $P = .005$ in tests 1 and 2, respectively).

As shown in Fig. 15.10, the intraindividual supine → standing changes in nHF were also related to the corresponding changes in heart rate ($P < .001$ for both comparisons in females, $P = .005$ and $P = .03$ for tests 1 and 2 in males, respectively). The corresponding slopes were also significantly different between females and males ($P = .001$ and $P = .002$ for tests 1 and 2, respectively). However, multivariable linear regression involving both age and the intraindividual heart rate changes as independent variables showed that age was the main determinant of nHF changes.

Interpretation

The data of the two studies show that in healthy middle-aged subjects, postural change from supine to unsupported sitting leads to averaged heart rate increases of approximately 10 bpm, while the change from supine to unsupported standing increases heart rate on average by approximately 30 bpm. While the extent of heart rate increases during postural change from supine to standing was not different between females and males in the first study and showed stronger reaction in males of the second study, HRV spectral analysis showed surprisingly larger decrease of normalized HF components in females compared to males. This was somewhat more marked in the second study that made the sex-related disparity between heart rate and nHF changes even more visible.

In both studies, females showed larger proportion of HF components at supine rest but when challenged with unsupported standing over 10–15 min, they decreased their HF components more than males so that the nHF difference between the sexes disappeared.

The shifts in the HRV components toward LF modulations on postural challenge have been established already some decades ago [18]. It became customary to interpret

TABLE 15.1 Heart rate and heart rate variability measurements in the first study.

		Heart rate	Total power	LF power	HF power	nHF
Test 1						
Supine	F	69.5 ± 8.2	2532 ± 2154	783 ± 678	759 ± 1206	0.426 ± 0.146
	M	64.6 ± 6.8	2406 ± 1604	824 ± 709	521 ± 541	0.359 ± 0.138
	p	<0.001	NS	NS	NS	<0.001
Sitting	F	79.2 ± 9.3	2215 ± 1496	777 ± 590	409 ± 506	0.315 ± 0.140
	M	73.7 ± 8.4	2457 ± 1505	963 ± 714	341 ± 326	0.255 ± 0.125
	p	<0.001	0.034	0.001	NS	<0.001
Standing	F	100.0 ± 14.1	1082 ± 861	434 ± 496	100 ± 102	0.199 ± 0.097
	M	92.9 ± 12.8	1445 ± 987	605 ± 524	137 ± 141	0.186 ± 0.111
	p	<0.001	<0.001	<0.001	0.009	NS
Standing	F	102.5 ± 14.5	1119 ± 832	434 ± 435	105 ± 100	0.198 ± 0.095
	M	95.4 ± 13.1	1453 ± 1106	622 ± 546	150 ± 179	0.190 ± 0.107
	p	<0.001	0.002	<0.001	0.012	NS
Supine	F	65.3 ± 8.0	3264 ± 3268	1031 ± 1058	1160 ± 1892	0.452 ± 0.155
	M	62.0 ± 7.1	2683 ± 2075	953 ± 860	649 ± 880	0.371 ± 0.135
	p	<0.001	NS	NS	0.012	<0.001
Test 2						
Supine	F	70.4 ± 7.4	2361 ± 1961	669 ± 528	659 ± 1017	0.426 ± 0.144
	M	64.6 ± 6.7	2241 ± 1424	743 ± 574	501 ± 559	0.365 ± 0.135
	p	<0.001	NS	0.033	NS	<0.001
Standing	F	97.2 ± 12.3	1085 ± 658	401 ± 335	112 ± 145	0.215 ± 0.101
	M	91.4 ± 11.7	1345 ± 768	555 ± 424	134 ± 181	0.187 ± 0.107
	p	<0.001	<0.001	<0.001	0.206	0.014
Standing	F	101.4 ± 13	1007 ± 697	376 ± 345	96 ± 94	0.204 ± 0.088
	M	94.5 ± 12.2	1303 ± 884	533 ± 440	133 ± 213	0.190 ± 0.111
	p	<0.001	0.001	<0.001	0.039	NS
Sitting	F	83.0 ± 9.2	1618 ± 1186	563 ± 471	298 ± 340	0.315 ± 0.134
	M	78.1 ± 8.7	1762 ± 1037	672 ± 450	246 ± 259	0.245 ± 0.118
	p	<0.001	0.024	0.001	NS	<0.001
Supine	F	72.2 ± 7.7	2013 ± 1717	648 ± 574	550 ± 662	0.414 ± 0.136
	M	67.7 ± 7.3	2001 ± 1563	699 ± 621	428 ± 588	0.340 ± 0.141
	p	<0.001	NS	NS	NS	<0.001

For different 5-min windows of both postural provocative tests of the first study, the table shows heart rate and spectral heart rate variability measurements in female (F) and male (M) study subpopulations. The data are mean ± standard deviation and for each 5-min windows, *P*-value (p) of the comparison between female and male subjects is shown. The 5-min windows of the standing position are shown in sequence as they occurred during the tests.

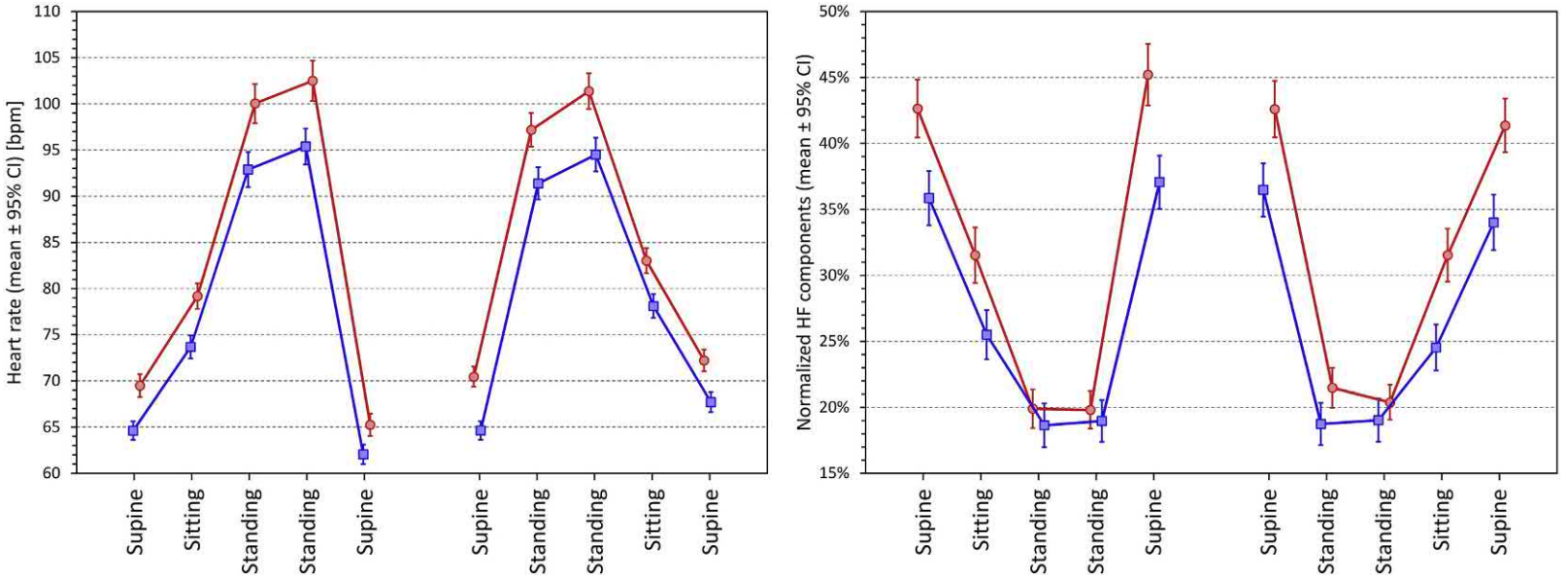

FIGURE 15.5 Measured values of heart rate (left panel) and of quasi-normalized high frequency HRV components (right panel) during prespecified 5-min windows of the postural tests of the first study. In each panel, the left and right parts correspond to the postural tests 1 and 2, respectively. The positions are listed under the panels (the order of the two standing positions corresponds to their sequence within the tests, see the text for details). In each panel, the *red and blue lines* correspond to female and male subjects, respectively. The *colored dots* show the means of the sex-specific subpopulation, the *error bars* show the 95% confidence intervals of the means. *Partly reproduced with permission from Hnatkova K, Šišáková M, Smetana P, Toman O, Huster KM, Novotný T, Schmidt G, Malik M. Sex differences in heart rate responses to postural provocations. Int J Cardiol. 2019. https://doi.org/10.1016/j.ijcard.2019.09.044.*

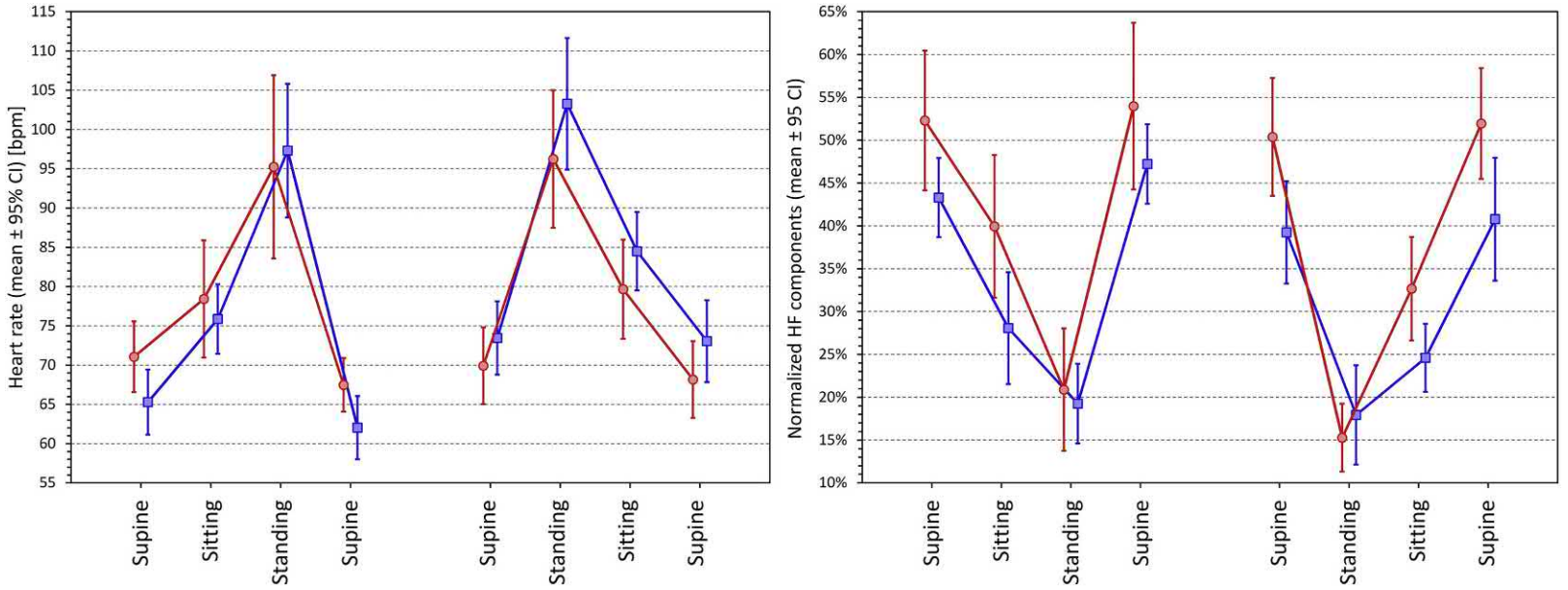

FIGURE 15.6 Measured values of heart rate (left panel) and of quasi-normalized high frequency HRV components (right panel) during prespecified 5-min windows of the postural tests of the second study. In each panel, the left and right parts correspond to the postural tests supine → sitting → standing → supine and supine → standing → sitting → supine, respectively. The positions are listed under the panels. In each panel, the red and blue lines correspond to female and male subjects, respectively. The *colored dots* show the means of the sex-specific subpopulation, the *error bars* show the 95% confidence intervals of the means. Compare with Fig. 15.5.

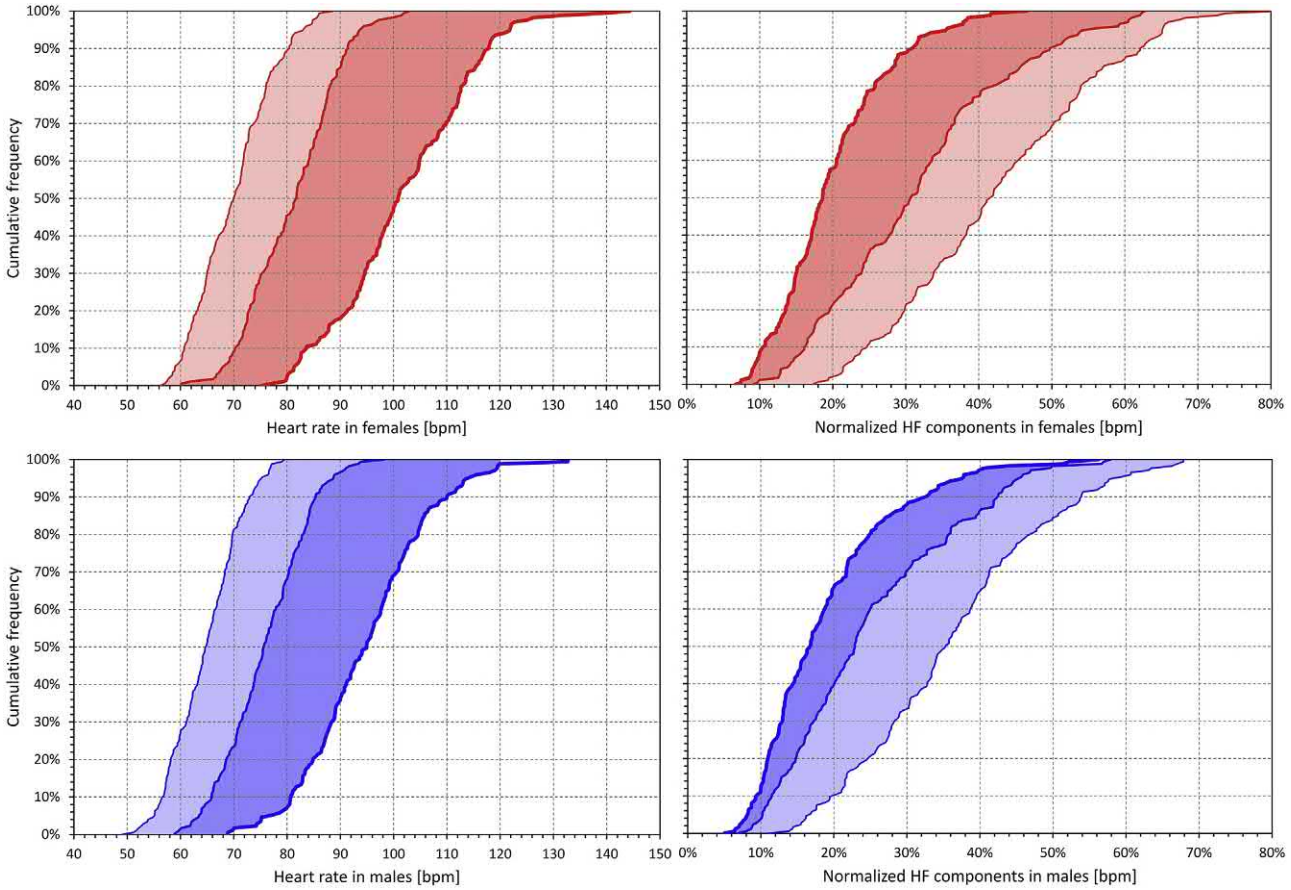

FIGURE 15.7 Cumulative frequency distributions of 5-min measurements of heart rate (left panels) and of quasi-normalized high frequency components (right panels) during initial supine positions (*fine lines*), sitting positions (*middle-width lines*), and final 5-min of standing positions (*bold lines*) of the first study experiments. The data presented are the intraindividual averages of both postural tests. The red and blue panels correspond to female and male subpopulations, respectively. *Light and dark shaded areas* highlight the shifts between supine and sitting positions and between the sitting and standing positions, respectively. Note that the extent of *dark shaded areas* is similar between the sex groups for heart rate but not for quasi-normalized high frequency heart rate variability components. *Partly reproduced with permission from Hnatkova K, Šišáková M, Smetana P, Toman O, Huster KM, Novotný T, Schmidt G, Malik M. Sex differences in heart rate responses to postural provocations. Int J Cardiol. 2019. https://doi.org/10.1016/j.ijcard.2019.09.044.*

these shifts in terms of cardiac autonomic status although the association between HRV indices and the autonomic tone is complex and not without limitations [19,20]. Undoubtedly, postural changes lead to changes in the autonomic status with shifts towards sympathetic dominance on standing. Hence, if interpreting the observed nHF changes using the customary model that links HF to primarily vagal modulations and LF to combined vagal and sympathetic modulations [17], the data might suggest not only that the described postural change from supine to standing leads to more pronounced sympathetic increase in females but also that the increased autonomic challenge imposed by standing eliminates the sex difference in baseline autonomic modulations.

As already discussed [14], sympathetic system of both human and other mammals is frequently characterized as responsible for "fight or flight" reactions while the vagal system has mainly calming role responsible for organism recuperation during rest [21]. It is therefore plausible to speculate that the baseline nHF sex difference and the more pronounced change due to physical provocation in females might be the autonomic conditioning basis for the sex differences in social behavior and stress responses [22,23] in which the "fight or flight" reactions are more pronounced in males, while female reactions are more of the "tend-and-befriend" category exhibited in response to threatening situations. Such sex-specific behavior is relevant for the protection of the social group and for offspring preservation.

The female "tend-and-befriend" reactions have also been described as persistent maternal characteristics unrelated to mental stress [24]. This is also well in agreement with our observations since we found statistically higher nHF values in females not only in supine but also in sitting

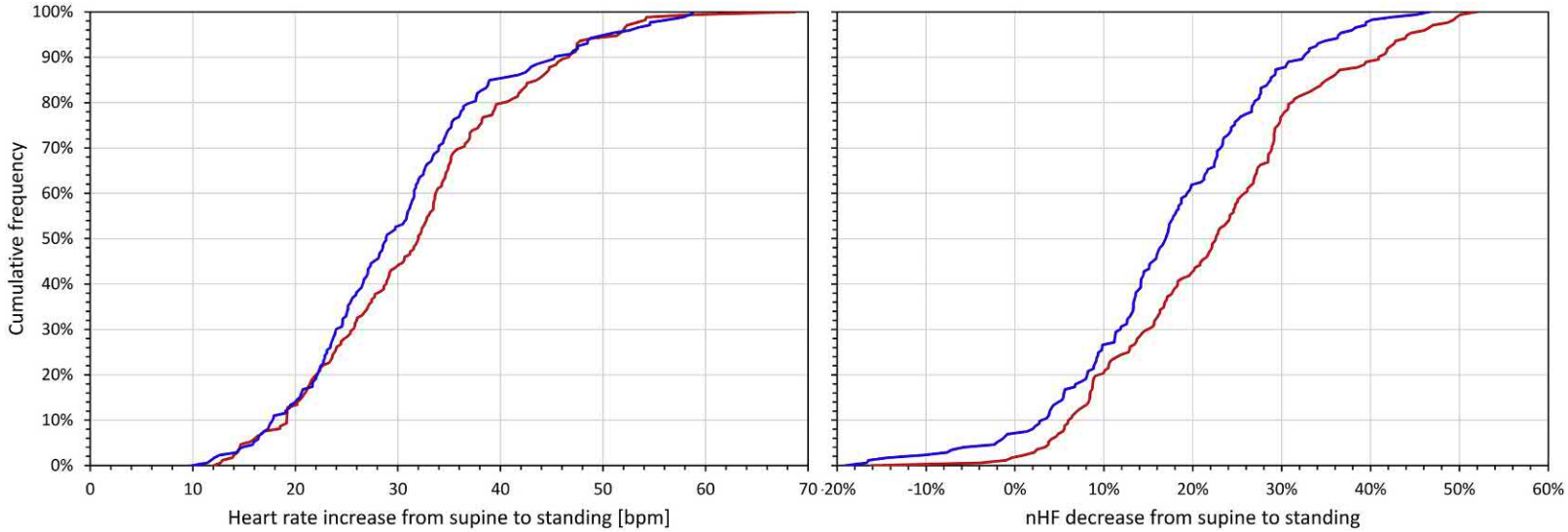

FIGURE 15.8 Cumulative distributions of changes of heart rate (left panels) and of quasi-normalized high frequency heart rate variability components (right panels) in the first study. The panels show the changes corresponding to the positional changes from supine to standing. The data presented are the changes of intrasubject averages of both postural tests; the data of the standing positions are taken from the final 5-min measurements. In each panel, *the red and blue lines* correspond to the female and male subpopulations, respectively. *Partly reproduced with permission from Hnatkova K, Šišáková M, Smetana P, Toman O, Huster KM, Novotný T, Schmidt G, Malik M. Sex differences in heart rate responses to postural provocations. Int J Cardiol. 2019. https://doi.org/10.1016/j.ijcard.2019.09.044.*

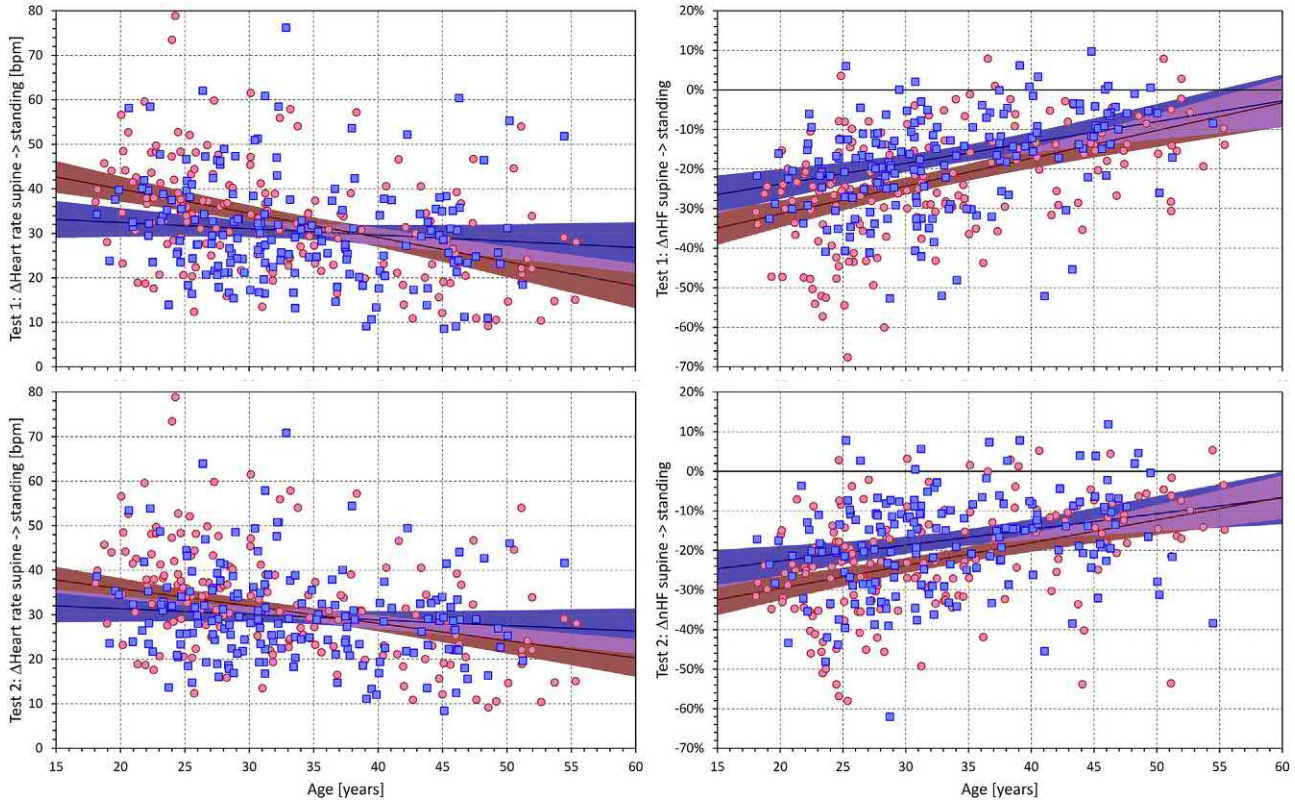

FIGURE 15.9 Scatter diagrams of age dependency of changes of heart rates (left panels) and of quasi-normalized high frequency HRV components (right panels) from supine to standing (final 5-min measurements) positions in the first study. The two rows of panels of the top part correspond to the postural tests 1 and 2, respectively. In each panel, the *red circles and blue squares* correspond to female and male study subjects, respectively. The *red and blue bold lines* show the linear regressions of the displayed data in female and male subpopulations, respectively. The *red and blue shaded areas* show the 95% confidence bands of the linear regressions, and the *violet areas* show the overall of the confidence bands of both sex-specific regressions. *Partly reproduced with permission from Hnatkova K, Šišáková M, Smetana P, Toman O, Huster KM, Novotný T, Schmidt G, Malik M. Sex differences in heart rate responses to postural provocations. Int J Cardiol. 2019. https://doi.org/10.1016/j.ijcard.2019.09.044.*

positions, i.e., after a change with only a mild sympathetic increase. More profound sympathetic stress of somewhat prolonged standing eliminated the sex difference. This might suggest that compared to males, female "fight or flight" responses might require stronger initiation triggers. This appears to agree with population data on sex differences in physical conflicts [25,26].

Since baseline sympathetic tone is also known to be potentially proarrhythmic, especially in patients without preexisting repolarization abnormalities [27], it is also plausible to speculate that the sex differences in the susceptibility to ventricular fibrillation [28,29] are contributed not only by sex hormones [28] but also by the differences in the baseline cardiac autonomic balance. This is also in agreement with our observation that the nHF sex differences were mainly present in younger age groups (note the convergence of the regression lines in the right panels of the left side of Fig. 15.9). Similarly, our observations of the sex differences in nHF reduction in response to substantial challenge might be relevant in interpreting the observations that among long QT syndrome type II patients, mainly females are at risk of arrhythmias induced by stimuli (e.g., abrupt awakening) that lead to substantial heart rate increases [30]. Nevertheless, it also needs to be added that since the majority of subjects of our study were relatively young and without any cardiac abnormality detectable at standard clinical screening [15], any speculations linking our observations to arrhythmic susceptibility need to be interpreted carefully and with caution.

Since the presented studies originated from clinical investigations of healthy subjects, it would be interesting to examine whether similar sex differences also exist in patients with cardiac and/or autonomic abnormalities, such as diabetic patients [31]. It would also be interesting to extend these investigations to healthy children or to the elderly of advanced age [32,33]. Along similar lines, the future research on the influence of menstrual cycle in females might provide further physiologic understanding of the link between menstrual cycle and autonomic reactions. Some HRV differences in different phases of menstrual cycle have previously been reported by some authors [34] albeit disputed by others [35].

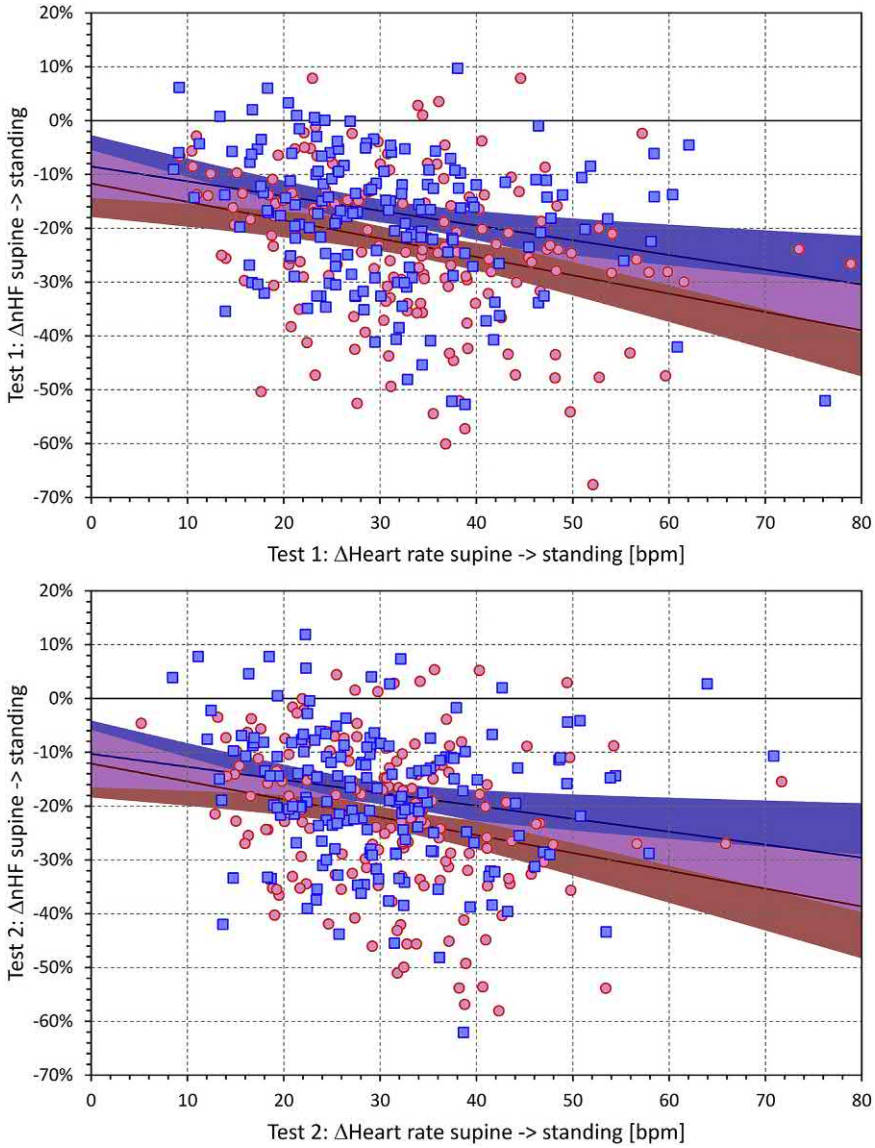

FIGURE 15.10 Scatter diagrams of the dependency between heart rate changes and of quasi-normalized high frequency heart rate variability component changes from supine to standing (final 5-min measurements) positions of the first study. The top and bottom panels correspond to the postural tests 1 and 2, respectively. The meaning of the symbols and the layout of the panels is the same as in Fig. 15.9. *Partly reproduced with permission from Hnatkova K, Šišáková M, Smetana P, Toman O, Huster KM, Novotný T, Schmidt G, Malik M. Sex differences in heart rate responses to postural provocations. Int J Cardiol. 2019. https://doi.org/10.1016/j.ijcard.2019.09.044.*

The ability of the postural tests to reveal the described sex differences suggests that similar autonomically active provocations might prove useful in a variety of physiologic studies [19,20] as well as in a broad spectrum of clinical investigations [29,36,37].

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Chapter 16

Sex and circadian pattern of autonomic status

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Introduction

The use of heart rate (HR) and heart rate variability (HRV) to characterize the status and functioning of the human autonomic nervous system has been well established, but the application of 24-h HR and HRV data to characterize circadian rhythms and to the question of differences by biological sex in circadian autonomic patterns has been extremely limited. A recent PubMed search on the term "heart rate variability" in human adults yielded 13,912 citations. Refining the search to "HRV" and "circadian" reduced this number to 820 citations. In these papers, sex is often part of the adjustment in a multivariate analysis, but the possibility of actual sex differences in the circadian rhythm of cardiac electrophysiology is rarely considered. To further complicate matters, age must be considered in any analysis of circadian HRV patterns. The addition of the term "sex" or "gender" to the PubMed search reduced the number of results to 70 citations, of which 11, reviewed here, were directly relevant to the question of differences by biological sex in the circadian rhythm of HR and HRV. Indeed, the perspective that markedly decreased values for 24-h HRV measures like SDNN (the standard deviation of all normal-to-normal interbeat intervals) are a signal for abnormalities in the circadian rhythm, or at least the diurnal rhythm, of autonomic functioning is generally lacking. The original paper from the Multi-Center Post-Infarction Project, published in 1987 [1], that caught the attention of the cardiology community by showing that among post-MI patients with a recent event (11 ± 3 days post), SDNN<50 ms was associated with an unadjusted risk of mortality 5.3 times higher than in patients with SDNN>100 ms over a mean follow up of 31 months and that this significant association of SDNN <50 ms and mortality persisted after adjustment for clinical and demographic covariates, was discussed in terms of a possible impairment in vagal function. The possibility that decreased SDNN is associated with circadian or diurnal abnormalities in cardiac autonomic functioning or that there could be a different cut point by sex was not considered.

Fundamentals of circadian rhythm

The suprachiasmatic nucleus (SCN) of the anterior hypothalamus has been firmly established as the master circadian pacemaker in mammals, although the cellular–molecular basis of circadian rhythm generation involves several circadian clock genes expressed not only in the SCN but also throughout the brain and peripheral tissues and organs [2]. Thus, the SCN serves as a central pacemaker, atop a hierarchically organized, anatomically distributed circadian timing system, and entrains downstream circadian clocks via neural and neuroendocrine pathways. This so-called "Master Clock" is designed to optimize synchronization of all systems in the body, including learning, memory and mood, and susceptibility to adverse events. The SCN circadian pacemaker is synchronized (entrained) by environmental light-dark cycles via photoreceptors and neural pathways distinct from those mediating visual perception. However, the assumption that this system is working in an integrated manner if there is a detectable circadian rhythm of HR or HRV is simplistic and potentially misleading. At the same time, system-wide circadian coordination is necessary for optimal physiologic function and maintenance of physical and mental health. It is for this reason that methods for distinguishing integrated versus more disorganized circadian rhythms, potentially using HR and/or HRV patterns, could provide an important clinical and research tool.

Circadian rhythms are designed to be synchronized to the physical environment, including responses to light and eating. It has been shown that most cardiovascular

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physiologic measures, and even cardiovascular events, have a circadian rhythm [3]. Differences by sex in circadian rhythms, as measured by timing of temperature and/or melatonin excretion, have been reported. In one such study, women were found to have a higher melatonin amplitude and lower temperature amplitude than men who were matched by habitual wake time [4]. Data were obtained during a constant routine protocol, which is an in-laboratory study where external drivers of circadian rhythm are masked. Also, large interindividual differences are present among people living in the same place and undergoing the same external circadian clues, *i.e.*, so-called morning people or "larks" and night people or "owls," and that there are important biological markers that distinguish them [5]. Furthermore, there are likely to be consequences in terms of the ability to adjust to changes in sleep wake routines and even, as has been shown in teenagers, for example, in the ability to learn when school starts too early in their circadian cycle [6]. The magnitude of HR and HRV measures also follows a circadian pattern, although changes are not necessarily synchronous. The potential for 24-h circadian HRV measures to provide insights into these aspects of circadian physiology and into the effect of sex on these biomarkers requires further exploration.

Nearly everyone is familiar with the effects of an acute dyssynchrony of circadian rhythm, namely jet lag. Jet lag and recovery from jet lag associated with a flight from Tokyo to Los Angeles was studied from the perspective of circadian rhythms of HR and HRV in 12 healthy young men [7]. Jet lag was found to be associated with a decreased period of the circadian rhythm. Moreover, with jet lag, the peak value for parasympathetic markers of HRV shifted from the normal early morning hours of sleep to the daytime. There are almost no other studies on circadian autonomic markers and jet lag.

Surprisingly, also, the use of 24-h HR and HRV measures to identify and treat other circadian rhythm disorders, which most clearly manifest as sleep problems like delayed sleep phase, advanced sleep phase, non-24-h, and irregular sleep-wake rhythm disorders [8], has not been extensively investigated, and the relationship of any findings to sex does not appear to have been reported. The importance of circadian and sleep disturbances to the health of the cardiovascular system, underscoring the need for chronobiomarkers to optimize timing of therapies and to study outcomes, is increasingly being appreciated [3,9], both in terms of hospital environments and the timing of therapies. However, the possibility that sex differences could be an important consideration has not yet been reported. While almost no studies have been conducted using 24-h Holter-based CAM (circadian autonomic measures) and their integration (i.e., relationship to circadian phase and relationship to each other) in order to characterize circadian rhythm disorders, such studies have a huge potential for identifying factors that disturb the integration of this rhythm and for developing and validating interventions that optimize human health. Also, since the circadian timing system, as previously noted, affects *all* aspects of physiologic functioning (Fig. 16.1), studies involving the collection of short-term HRV measures might potentially be affected by both the sex of the participant and the time of day that the data were collected.

How can circadian autonomic modulation be assessed and quantified?

Graphical representations

Although the circadian rhythm of electrophysiological parameters can be assessed in terms of changes in the characteristics of the QRS itself (e.g., changes in QRS characteristics like the QT interval), the current review will be limited to the use of HR and HRV changes as a surrogate for CAM. Simultaneous analyses of circadian rhythms of HR and circadian rhythm of other HRV parameters, as a marker for circadian autonomic integration, have barely been explored, and normal values of these relationships for age and sex have not been described. In its simplest form, circadian rhythms can be appreciated from a simple plot of HR versus time. Graphical plots demonstrate, but do not quantify, circadian rhythms. However, as shown in Fig. 16.2, abnormalities, e.g., failure of HR to dip at night and abnormalities of other circadian HRV parameters, can often be clearly seen from the results of 24-h Holter analysis. Fig. 16.2A is a plot of 24-h 5-min averaged values for HR (upper right), LF/HF ratio (upper left), HF power (lower left), and the center frequency of the HF peak (a surrogate for the respiratory rate, lower right) in a cognitively normal older adult. Bed and wake times are also clearly seen and indicated in a consistent manner across panels, although the LF/HF ratio for wake time is not obvious and has not been marked. Fig. 16.2B is a plot of the same 24-h patterns in an older adult with dementia. As can be seen, circadian HR and HRV patterns are clearly abnormal in this person and bed and wake times cannot be identified from the plots. It should be noted that the y-axis for each panel, except for center frequency of the HF peak, is scaled for the individual recording.

Statistical comparisons of HR or HRV during selected time periods

Statistical comparisons of hourly HR and HRV, HR and HRV during selected time periods, or day versus night have also provided insights into sex differences in diurnal changes in CAM by sex. A limitation of this approach, especially of the day versus night analysis, is that daytime and nighttime are approached as fixed times, *e.g.*, nighttime

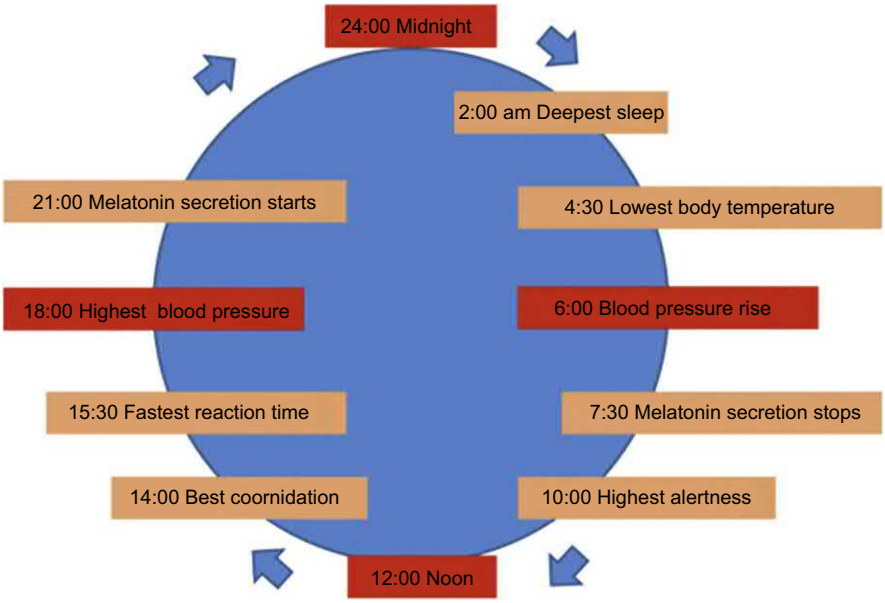

FIGURE 16.1 Schematic illustration representing circadian changes in biomarkers and functioning with time of day.

is often 00:00–05:00, and there is an assumption that most subjects are asleep during that time, or even if asleep that comparable sleep stages are being captured. Furthermore, subjects with sleep-disordered breathing (SDB), which can be detected from HR patterns during sleep [10], are being compared to subjects without sleep-related breathing disorders, and both the repeated arousals and changes in respiratory rate during SDB events have a significant effect on HR and HRV.

Cosinor analysis

Cosinor analysis fits the individual circadian/diurnal rhythm of a set of measurements to a cosine function and extracts three values: M, the mean or MESOR of the fitted amplitudes; A, the peak amplitude; and Θ, the acrophase or timing of the peak amplitude relative to a fixed time (Fig. 16.3). Cosinor analysis is applicable to any periodic process and been shown to be applicable to CAM [11]. This technique could potentially support the extensive literature on circadian rhythm disorders and their management [2]. A review by Sammito et al., in 2016 [12], also clearly demonstrated the circadian nature of HRV measures, based on 26 studies. Sex differences in these circadian patterns were not addressed in their review.

Papers specifically addressing sex differences in circadian rhythm of HR and HRV

Reports of differences in 24-h HRV between sexes are plentiful. The consensus of the vast majority of them is that women, at least until older age, have higher HRs and lower total HRV (*e.g.*, SDNN or total spectral power), but higher values for vagally modulated HRV than men. A recent metaanalysis by Koenig and Thayer, published in 2016 and based on 172 qualifying studies, fully describes this literature [13]. However, in our search of the literature, only 11 papers *specifically* assessing sex difference in circadian (or diurnal) rhythm of cardiac autonomic modulation, with an awareness of the potential interaction between age, sex, and CAM, were located. They are described below.

One of the earliest reports of age and sex differences in circadian HRV was published in 1996 by Yamasaki et al. [14]. N = 105 healthy volunteers had 24-h Holter recordings and frequency domain HRV analysis of each 512 consecutive N–N interbeat intervals was performed. High-frequency (HF) spectral power, low-frequency (LF) spectral power, LF + HF power, and the % LF power (LF/LF + HF) were determined for each segment. Diurnal profiles of HRV were reported as averaged values for 24 h, for the morning (08:00–12:00), afternoon (12:00–18:00), evening (18:00–24:00), night (00:00–06:00), and early morning (06:00–08:00) periods and compared both by age and sex. A consistent increase in HF power during sleep (at night 00:00–06:00) was seen for all subjects. Reports of differences by sex included a finding that males had significantly higher LF power from 08:00–12:00, whereas females had higher LF power from 12:00–24:00. When the effect of age group was considered, heterogeneous difference by sex was seen, but the small number of subjects in each age–sex subgroup (range 7–18) makes it difficult to generalize these findings. Bonnemeier et al., in 2003 [15], compared hourly values and mean 24-h values of time

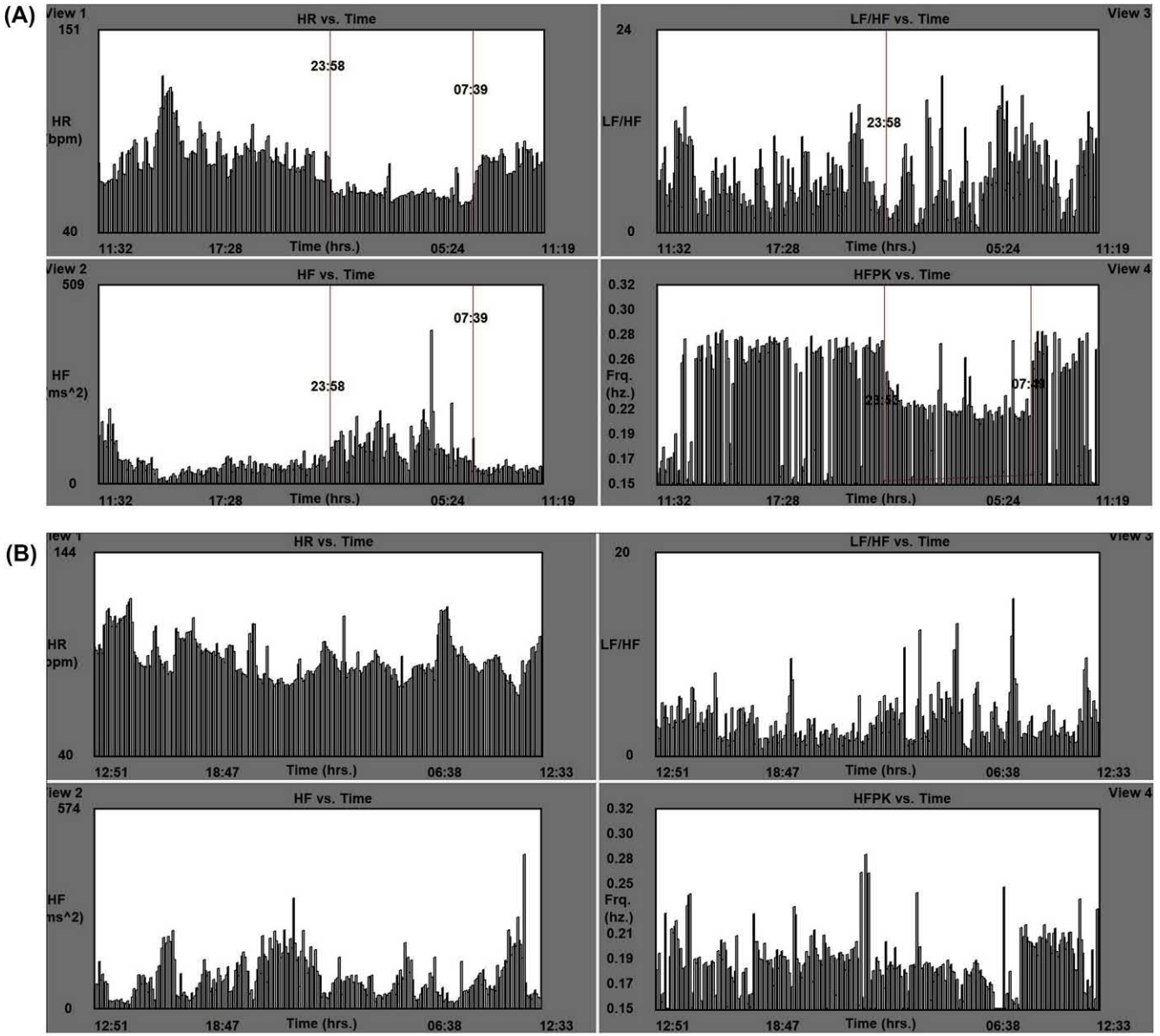

FIGURE 16.2 Comparison of circadian patterns of HR, LF/HF ratio, HF power, and the center frequency of the HF peak in (A) a cognitively normal older adult and (B) an older adult with dementia.

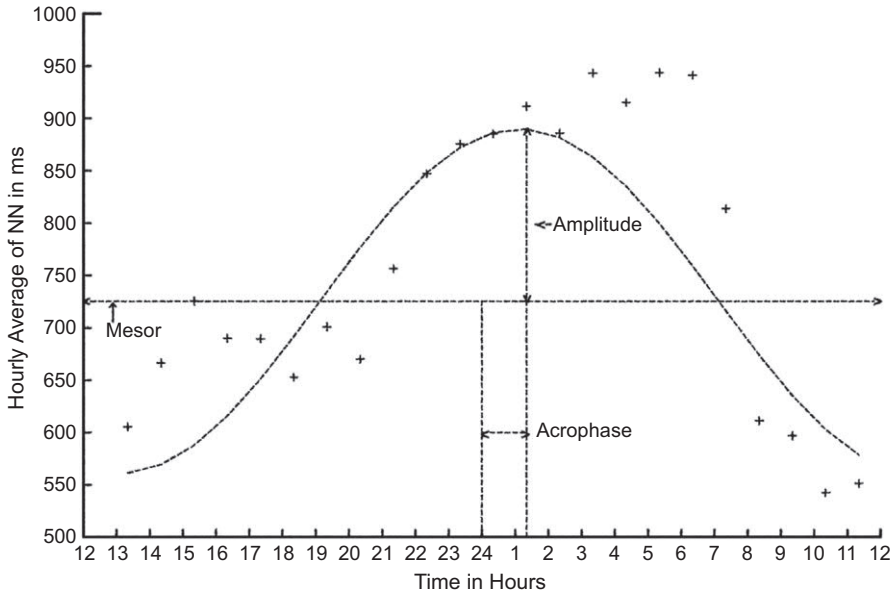

FIGURE 16.3 Cosine function fitted to a plot of averaged NN versus time over 24 h. *From Reference Zee PC, Attarian H, Videnovic A. Circadian rhythm abnormalities. Continuum(Minneap Minn) February 2013;19(1 Sleep Disorders):132–147. http://doi.org/10.1212/01.CON.0000427209.21177. [aa. Review.PMID].*

domain HRV in N = 81 women and N = 85 men with ages ranging from 20 to 70, all free of cardiac disease. They confirmed that circadian parameters of vagally associated HRV had a nighttime peak and that the day-to-night difference decreased by decade of age. They saw an increase in hourly values for long-term HRV parameters (e.g., SDNN) in the morning. Values for all 24-h HRV measures also decreased with advancing age. Men continued to have higher values for SDNN, SDNNi (averaged SDNN for each 5 min), and SDANN (standard deviation of the 5-minaverages of SDNN). Significantly higher values for vagally modulated HRV parameters were found in the younger men, but sex differences in these parameters decreased with advancing age.

On the other hand, it must be noted that a study published in 2005 by Bilan et al. [16], involving 76 healthy volunteers aged 35–55 years, confirmed that hourly values for LF, HF, and LF/HF showed a circadian pattern, consistent with what was reported by others (although LF and HF were not ln transformed in their analysis, as is generally done, which resulted in wide confidence intervals and may have limited statistical power). Morning, day, and night periods were compared separately. Sex was adjusted for statistically and only a trend for 24-h LF power to be greater in males was observed.

Cosinor analysis, described above, has permitted a detailed comparison of CAM patterns between sexes. Li et al. [11] compared CAM between sexes, using 24-h, 12-lead Holter recordings in a sample of 115 community-dwelling, nonsmoking adults living in Central Pennsylvania and participating in the Air Pollution and Cardiac Risk and its Time Course study. assessed using 5-min averaged values of SDNN, rMSSD (root mean square of successive differences in N–N intervals), ln LF (0.04–0.15 Hz) and ln HF (0.15–0.40 Hz) spectral power, and their ratio (LF/HF ratio). Data were fitted to a cosine curve for each individual and cosinor analysis was used to quantify circadian variation. Their basic findings, as previously mentioned, were that cosinor analysis *could* be used to quantify circadian HR and HRV measures. LI et al. also reported that results were a function of age, with older adults having lower HRV and a later acrophase of the LF/HF ratio than younger ones. When sex was considered, males had higher amplitudes of circadian HRV than females and a later acrophase, by almost 3 h, of the LF/HF ratio, but no other difference were found in this relatively small sample.

The HRV effect of shift work provides a naturalistic environment in which to compare aspects of circadian HRV between sexes. Hulsegge et al. [17] reported that shift work was associated with reduced HRV among men but not women. N = 665 blue-collar workers aged 18–68 from two Danish cohort studies were studied. An Actiheart monitor was used to collect 24-h HR data for assessment of time and frequency domain HRV during sleep. The investigators compared HRV between day and shift workers. Results, after multivariate adjustment, indicated that for most measured HRV (i.e., rMSSD, SDNN, VLF [very–low-frequency spectral power: 0.0033–0.04 Hz]) and total power, male, but not female, shift workers had significantly

lower HRV at night than nonshift workers. Among female night shift workers, only the LF/HF ratio was significantly lower at night. Results were extrapolated to the possibility that this difference might be associated with a greater risk of CVD among men.

Almost all of the published studies of circadian HRV and sex have relied on HR or standard time or frequency domain HRV measures. Vandepurt et al. [18] undertook a reanalysis of an existing dataset of 135 healthy women and 141 healthy males who were recruited from three Belgian centers. Differences by sex in HRV parameters in this cohort had already been reported by Ramaekers et al. in 1998 [19], and no difference in HRV parameters reflecting vagal modulation of the heart were found after adjustment for HR and the age-related decline in all HRV. Sex differences were found only in subjects under 40 years of age. Beckers et al. [20] reanalyzed data from the same cohort in 2005. They compared multiple nonlinear HRV parameters during the daytime (8 a.m.—9 p.m.) and nighttime (11 p.m−6 a.m.). Day-to-night differences were seen in virtually all nonlinear HRV parameters, except for one (the correlation dimension) among females. All measures were significantly correlated with age, but no difference by sex was seen. In the Vaneput et al. reanalysis, the circadian profile of multiple nonlinear HRV measures was compared between men and women. A clear circadian pattern for virtually all nonlinear measures was seen and that pattern was similar by sex. Results are too complicated to describe in full, but briefly, higher HRs were seen in women than in men, as reported in other studies, and women also showed higher values for most nonlinear HRV measures, but not for those considered markers for chaos. Sex differences in certain specific parameters were seen during the daytime or nighttime only.

Differences by sex in the relationship of the circadian pattern of HRV and mood

As mentioned above, the functioning of *every* system in the body, including mood, is controlled by the circadian pacemaker. The relationship of sex and circadian HRV in association with mood was explored by Jarczok et al. [21]. They used cosinor analysis to examine the circadian pattern of rMSSD, taken as a marker for vagal modulation of HRV. Retrospective data from 24-h Holter recordings in 3030 predominantly healthy working adults who also had detailed health examinations and filled in an online questionnaire were available. Three individual-level cosine function parameters (MESOR, amplitude, acrophase) were calculated in order to quantify circadian variation patterns. Results were adjusted for age, sex, and lifestyle factors, using multivariate linear regression models. Importantly, the interactive effect of sex with depression symptoms was used to examine the relationship circadian patterns of rMSSD and depressive symptoms by sex. Jarczok et al. found that depressive symptoms were associated with a decreased circadian variation pattern of vagal activity in men, but with an *increased* circadian variation pattern in women. The possible underlying mechanism(s) were discussed using the neurovisceral integration model [22], which summarizes the relationship between the central nervous system and HRV. These findings may have implications for the understanding of the etiology, diagnosis, course, and treatment of depressive symptoms and thus may have significant public health relevance.

A second study of sex, circadian HRV, and mood was published by Verkuil et al. in 2015 [23]. Depression has been clearly related to adverse cardiovascular outcomes [24]. Yet, studies have shown that among women, depression is associated with higher levels of some HRV parameters. The purpose of the Verkuil et al. study was to test whether there was a relationship of sex with rMSSD from 24-h ambulatory recordings and depressive symptoms, assessed hourly using the Center for Epidemiologic Studies Depression scale. Results showed a relationship between average daily sadness and rMSSD in women but not in men. Specifically, the total amount of sadness experienced during the day was associated with higher circadian levels of rMSSD only in women.

Sex effect of interventions on circadian HRV

Very little has been written about the effect of interventions on the relationship of sex and circadian CAM. However, Fürholz et al. [25] studied the sex effect of endurance training among runners training for a 10-mile race. $N = 68$ females and $N = 79$ males were randomly selected from among 873 applicants. Runners were stratified according to their average weekly training hours into a low- ($\leq$4 h) and high-volume (>4 h) training group. HRV was calculated from 24-h recordings. HRV measures included HF power and LF power in normalized units, calculated for each 5-min segment and averaged for each hour. Daytime and nighttime hourly HRV averages were compared between groups. No significant differences were seen between females and males for training volume or 10-mile race time. However, female athletes had higher HF and lower LF power for each hourly time point. Also, among the female athletes, higher training load was associated with similar patterns of higher HF power and lower LF power during the nighttime. Among the male athletes, higher training volume was also associated with higher HF and lower LF during the daytime, but *not* during the nighttime. Thus, female athletes seemed to have a higher level of presumably cardioprotective, vagally modulated HRV for the same

training volume. The authors suggest that this difference in circadian adaptation to training might help explain the male predominance in risk of sudden death among athletes because endurance training results in female athletes having superior protection against exercise-induced ventricular arrhythmias.

Summary and recommendations

It is clear that differences, by sex, in the circadian rhythm of electrocardiography markers and the consequences of these differences have barely been explored. The importance of considering sex differences in all aspects of cardiovascular research was emphasized in the recent commentary by Merk Woodward [26]. At the same time, there is a huge, unexplored database of already-collected, analyzed, and stored 24-h ECGs that could be reanalyzed from this perspective, both in epidemiologic studies and from stored clinical data that could expedite research in this area. Furthermore, in most cases, bed and wake times can be identified from HR and HRV patterns on a 24-h recording, as shown in Fig. 16.2A, so the current limitation of assuming a fixed sleep time for all subjects can usually be overcome and the effect on results, if any, of using a prespecified sleep time, can be evaluated. Some studies have serial Holter recordings at intervals on the same participants (e.g., the Cardiovascular Health Study that has recordings at baseline and 5 years later on a subcohort of older adults), which could provide further insight into the effect of age of the differences by sex in CAM. Finally, it is important to emphasize that the assumption that increased values for rMSSD or HF power *always* reflect increased vagal activity needs to be addressed. Just as higher values for SDNN capture more variation over 24 h, they do not necessarily reflect a more normal *circadian* rhythm because SDNN does not capture the circadian organization of the HR pattern. Similarly, higher values for rMSSD or HF power can be seen in the presence of an "erratic" or disorganized short-term sinus rhythm, which can be detected using graphical methods, *e.g.*, a tachogram of instantaneous HR versus time or the appearance of the power spectral plot or from abnormalities in nonlinear HRV parameters (e.g., DFA $\alpha 1$ that characterizes the regularity of HR patterns on a scale of 4−11 beats or SD12, the ratio of the axes of an ellipse fitted to a scatterplot of each N−N interval vs. the next) that capture the organization of the interbeat intervals [26]. However, the appearance of an abnormally organized sinus rhythm could be the result of scanning error (uneven beat detection) rather than an abnormality in HRV itself, which underscores the importance of research quality scanning, or at the very least, access to the original ECG signal to validate vagal measures of HRV when their organization is in question. A similar issue applies HR patterns to non−ECG-detected HRV measures from portable pulse-based devices where validation against the actual signal is not possible.

Finally, although it has not been customary to consider the time of day when short-term HRV data are collected, e.g., 10 min resting HRV or the HRV response to a stressor, and in studies where tests are repeated after an intervention, the finding of differences by sex in circadian HRV supports the importance of ensuring that the retest data were collected during the same time period. The possibility that the CAM effect of an intervention, even in short-term data collections, would be different in men and women suggests that future studies of short-term HRV should be required, by reviewers, to take this into consideration. Also, when information about the time of data collection is available in previously collected datasets, results, if possible, should be reviewed from the perspective of a possible interaction between the sex of the participant and the circadian phase of data collection.

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Part V

Effects of sex hormones

Chapter 17

Electrophysiological cellular effects of sex hormones

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Introduction

Women are known to be more susceptible to long-QT syndrome and related arrhythmias, namely *torsades de pointes* [1], also in relation to use of various drugs, both cardiac and noncardiac (for a review see Ref. [2]). On the other hand, the incidence of Brugada syndrome and related arrhythmias is higher in men [3]. Sex differences in the susceptibility to arrhythmias were also demonstrated in experiments on various animal species, including rabbit [4] or dog [5]. Some of the sex-specific features of cardiac electrophysiology underlying the varying susceptibility of men and women to various types of arrhythmias have been already revealed, as will be discussed in this chapter. Gaps in the knowledge will be identified.

Sex hormone–induced changes of action potential configuration in cardiomyocytes

Action potential (AP) represents characteristic pattern of changes of the membrane voltage in excitable cells. In the muscle cells including cardiomyocytes, it serves as a stimulus starting mechanical activity (contraction) of the cell. The AP waveform of working atrial and ventricular cardiomyocytes is composed of five typical phases: depolarization, early repolarization, plateau, final repolarization, and phase of the resting membrane potential (phase 0–4, respectively; Fig. 17.1). These phases have to proceed within physiological limits to keep regular pattern of the cardiac depolarization and repolarization, thus to provide proper contraction of the heart. Impairment of any of these AP phases may lead to occurrence of arrhythmia, thus potentially to death.

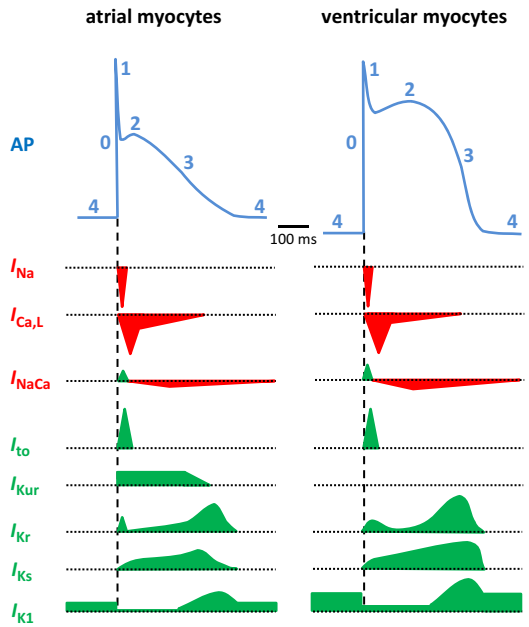

FIGURE 17.1 5Scheme of action potential (AP) waveforms and main underlying ionic membrane currents in atrial (left panels) and ventricular (right panels) myocytes; 0, 1, 2, 3, and 4—phases of AP, namely depolarization, early repolarization, plateau, final repolarization, and phase of the resting membrane potential, respectively; I_{Na}—sodium current, $I_{Ca,L}$—L-type calcium current, I_{NaCa}—sodium–calcium exchange current, I_{to}—transient outward potassium current, I_{Kur}—ultrarapid delayed rectifier potassium current, I_{Kr} and I_{Ks}—the rapid and slow components of delayed rectifier potassium current, respectively, and I_{K1}—inward rectifier potassium current. Depolarizing currents are denoted in red, whereas the repolarizing ones in green. I_{NaCa} seems to be mostly depolarizing current during the cardiac AP, contributing to extrusion of Ca^{2+} from the cytoplasm. I_{Kur} is mostly expressed in the atrial tissue, thus its contribution to the ventricular repolarization is negligible.

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Expression of both estrogen and progesterone receptors was proved in rat neonatal cardiomyocytes; their expression moreover increased after application of estradiol [6]. Later, expression of the estrogen receptors was confirmed in cardiomyocytes of other species including human (e.g., Refs. [7,8]; for a recent review, see Ref. [9]). Estradiol was shown to increase expression of the progesterone receptors in cultured female human atrial cardiomyocytes [10]. Androgen receptors were also reported to be expressed in the myocardial tissue, both in the developing rat heart [11] and in the adult heart of various species including human [12]. Thus, a direct effect of sex hormones on the cardiac electrophysiology may be expected.

The QTc intervals are known to be longer in adult women than in adult men, at least until the age of around 50 (e.g., Ref. [13]). In agreement, the AP duration (APD) has been often reported to be longer in the female ventricles of various species (e.g., dog [5,14]; guinea pig [15]; rabbit [16]; mice [17]; mice expressing human SCN5A channels [18]; human [19]; Fig. 17.2 A and B). Bai et al. [20] demonstrated that the acute application of testosterone shortened APD in guinea pig ventricular myocytes, even at physiologically relevant concentrations. Opposing studies showing no significant sex differences in APD have been rarely published as well (e.g., rat [21]). Other parameters describing the AP configuration (beside APD) are not usually mentioned in the studies that may predict that they do not show substantial intersex differences. It was confirmed in human cardiomyocytes by Verkerk et al. [19].

Changes of cardiac ionic channels/currents induced by sex hormones

A fine balance between depolarizing (mostly sodium and calcium) currents and repolarizing (mostly potassium) currents keeps appropriate APD (Fig. 17.1) and, thus, effective refractory period (ERP) in cardiomyocytes, preventing formation of arrhythmogenic substrate. Both shortening and prolongation of ERP may result in arrhythmia.

Considering the reported delayed repolarization in female ventricles (see Section Sex hormone–induced changes of action potential configuration in cardiomyocytes), an

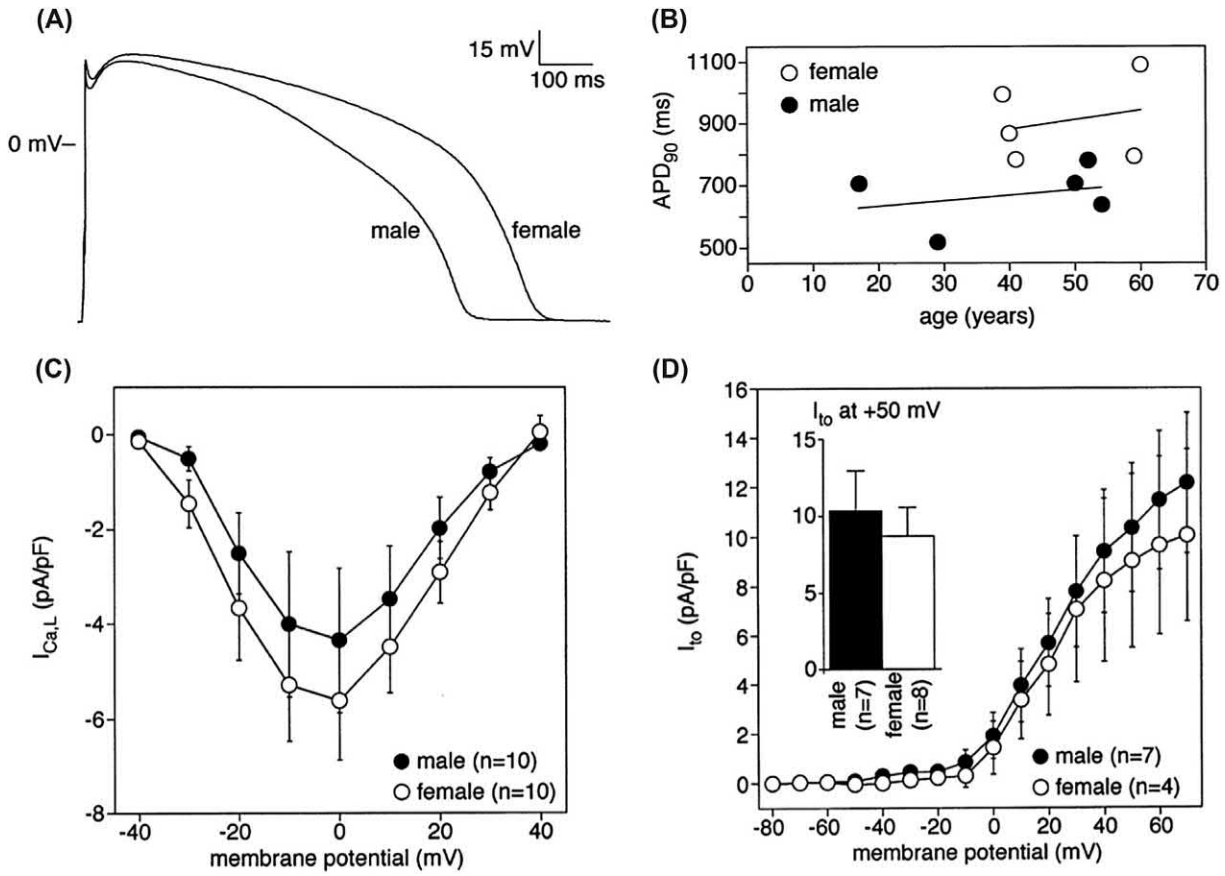

FIGURE 17.2 Basic electrophysiological characteristics of human failing left midmyocardial cardiomyocytes. (A) Action potential configuration in representative male and female cardiomyocytes. (B) Dependence of action potential duration at 90% repolarization (APD90) on the age of the respective patient. (C and D) Density of L-type calcium current ($I_{Ca,L}$) and transient outward potassium current (I_{to}), respectively, in the investigated cells. *Reproduced with permission from Verkerk AO, Wilders R, Veldkamp MW, de Geringel W, Kirkels JH, Tan HL. Gender disparities in cardiac cellular electrophysiology and arrhythmia susceptibility in human failing ventricular myocytes. Int Heart J 2005;46(6):1105–18.*

impaired balance between the depolarizing and repolarizing forces may be expected during the female ventricular AP, especially during the AP plateau and final repolarization. Relevant data on the sex differences in particular ionic currents published so far will be discussed in the following subchapters.

Voltage-gated sodium channel

Few and diverse data are available on sex differences in the channels conducting depolarizing fast sodium current I_{Na} (formed namely by the Nav1.5 α-subunit in the human heart). Barajas-Martinez et al. [22] reported a larger dispersion of I_{Na} in the female canine left ventricle with a smaller I_{Na} amplitude in subepicardial and subendocardial layers (but not in midmyocardium) in comparison with the male tissue; the female subepicardial I_{Na} increased after exposure to testosterone. In contrast, no changes of the protein expression level and current were apparent in a cell line expressing Nav1.5 and sex hormone receptors after the line was exposed to sex hormones [23].

The late sodium current $I_{Na,L}$ (i.e., the moiety of I_{Na} with slow inactivation) was increased in female ventricular myocytes of mice expressing human SCN5A channels [18]. In contrast, the rabbit $I_{Na,L}$ was larger in male left atrium posterior wall in comparison with the female tissue and comparable in the right atria of both sexes [24].

Voltage-gated calcium channels and Ca^{2+} handling mechanisms

Most studies have revealed that adult female ventricular cardiomyocytes show a higher depolarizing L-type calcium current ($I_{Ca,L}$; formed namely by the Cav1.2 α-subunit and the modulatory Cavα2δ and Cavβ2 subunits in the human heart; Fig. 17.1). It was demonstrated for both the left ventricle (e.g., rabbit [4,25], guinea pig [15], rat [26], dog [14], and even human failing cardiomyocytes [19]; Fig. 17.2C) and also for the right one (rabbit [27]). $I_{Ca,L}$ seems to be preferentially increased at the ventricular base [4,25,27]. Pham et al. [28] demonstrated a higher $I_{Ca,L}$ density in the female rabbit subepicardium than in the subendocardium; similar difference was absent in the male rabbit heart. The changes of $I_{Ca,L}$ are likely caused by changes in expression of the Cav1.2 subunits because it was demonstrated to be higher in female than in male in various species [4,25,26,29] including human [30]. In human-derived cardiomyocytes, Papp et al. [30] have demonstrated that 1- to 2-day exposure to 1 nM estradiol can increase $I_{Ca,L}$ by 31% if these cells are originally female, but not if they are of the male origin.

Beside the long-term effects, sexual hormones exert acute effects on $I_{Ca,L}$ as well; the character is usually, but not always (see later), consistent with the long-term effects. Acute administration of estradiol was demonstrated to increase $I_{Ca,L}$ density [31,32], whereas progesterone decreased it in the rabbit heart [32]. Acute administration of testosterone at physiologically relevant concentrations rapidly shortened APD through nongenomic suppression of $I_{Ca,L}$ in guinea pig ventricular myocytes, mediated by an increase of cytosolic concentration of nitric oxide (NO [20]); I_{Ks} was concurrently enhanced (for more, please see Section Voltage-gated potassium channels). As later demonstrated by Er et al. [33], 24- to 30-h presence of testosterone caused opposite effect, i.e., activation of $I_{Ca,L}$. However, this prolonged effect was completely reversed during acute application of testosterone that induced $I_{Ca,L}$ suppression [33], in agreement with previous data by Bai et al. [20].

The increase of $I_{Ca,L}$ was simulated to prolong APD and, in combination with diminished repolarizing currents, to promote early afterdepolarizations (EADs) [4,19,27,34]. Analogical observation was reported in experiments on human failing female cardiomyocytes [19].

In contrast, some other studies reported comparable $I_{Ca,L}$ in female and male (e.g., in the rat ventricle [35,36], in the rabbit atrium [24], in the mouse ventricle [37]) or even lower $I_{Ca,L}$ in female (e.g., in the guinea pig ventricle, but $I_{Ca,L}$ was larger during oestrus than during postoestrus [38]).

Expression of the T-type calcium channel ($I_{Ca,T}$; formed by the Cav3.1 and Cav3.2 α-subunits in the human heart, namely in the sinoatrial and atrioventricular nodes) did not show any sex-related differences in the human ventricular tissue [39]. Unfortunately, data about expression of this channel in male and female in a more relevant nodal cardiac tissue seem not to be available in the literature.

In line with the usually reported increase of $I_{Ca,L}$, the depolarizing sodium−calcium exchange current (I_{NaCa}; Fig. 17.1) seems to be also increased in female [30,40]. The increase was again preferentially observed at the base in the rabbit heart [40]. I_{NaCa} is upregulated by a genomic mechanism mediated by estrogen receptors [30,40]. A 7.5-fold increase of I_{NaCa} was observed in female human-derived cardiomyocytes after 1- to 2-day exposure to estradiol; in contrast, I_{NaCa} was not altered under these conditions in male human-derived cardiomyocytes [30]. According to these data, it seems that changes of $I_{Ca,L}$ and I_{NaCa} proceed along which provides a proper balance between influx and efflux of Ca^{2+} in cardiomyocytes [41].

In contrast, diverse data were reported in the rabbit atrial tissue where both $I_{Ca,L}$ and I_{NaCa} were comparable in male and female (surprisingly, the Ca^{2+} transient and SR Ca^{2+} content were larger in male than in female [24]).

Some other Ca^{2+}-handling mechanisms also differ between female and male. Since this is behind the scope of this chapter, only basic facts will be mentioned here. Data from various studies substantially differ, maybe due to

interspecies differences or other varying experimental conditions. For example, an increased expression of Ca^{2+}-ATPase 4 (SERCA4) and calmodulin-3, and a decreased expression of phospholamban were reported in the human female healthy myocardial samples in comparison with the male samples [39]. However, no sex differences in SERCA2a and phospholamban were observed in animal models (e.g., in rat [29,42], in rabbit [43]). In orchiectomized rats, testosterone was even shown to increase SERCA activity (orchiectomy significantly decreased the phosphorylated form of phospholamban [44]). The resulting Ca^{2+} transients are mostly reported to be smaller in adult female (e.g., Refs. [36,37,45]), namely in the case of rapid pacing rates. However, no significant difference in the baseline Ca^{2+} transients between sexes was also observed in various species (e.g., in rabbit [43], in mice [46], in rat [35,47]). The results may be also affected by the age of animals. As reported by Grandy and Howlett [46], the Ca^{2+} transients and the mean systolic and diastolic concentrations of Ca^{2+} were all comparable in young adult mice of both sexes, but they were smaller in aged male mice than in aged female mice. Unfortunately, data revealing sex-related differences in the Ca^{2+} transients in healthy human ventricular myocytes or myocytes of animals closer to human than rodents are not available.

Blunted β-adrenergic electrophysiological and contractile response was observed in female ventricular myocytes of various species (e.g., Refs. [26,43,48–50]). It was accompanied by a reduced arrhythmic activity in female rabbit hearts [50]. As observed in mice female hearts, the blunted β-adrenergic contractile response likely arose from minor differences in effects of adenylyl cyclase and A1 adenosine receptor [49]. Tsang et al. [48] demonstrated that the enhanced contractility in the rat male heart during stimulation of adrenergic receptors results from an increased Ca^{2+} release through the ryanodine receptors. It was accompanied with a faster relaxation resulting from faster Ca^{2+} removal through SERCA and I_{NaCa}. All these testosterone effects were mediated through the androgen receptors. Parks et al. [37] revealed that the reduced Ca^{2+} transient is accompanied by lower basal levels of the cyclic adenosine monophosphate (cAMP) in the female mice ventricular myocytes, at least in part due to higher expression of phosphodiesterase type 4B. Moreover, the isoproterenol-induced increase of cAMP was also diminished in female rat ventricular myocytes [26]. Hence, modulation of contractility, especially by the protein kinase A pathway, seems to substantially differ in male and female.

The proarrhythmic tendency in women varies during the menstrual cycle and pregnancy. The repolarization was significantly accelerated during the luteal phase in healthy women, when both progesterone and noradrenaline levels were increased [51]. Progesterone was shown to exert antiarrhythmic effect by accelerating cardiac repolarization, whereas estradiol was documented to promote arrhythmias through an opposing effect [32,52,53]. Progesterone was also reported to protect against deceleration of repolarization associated with inhibition of potassium channels in rabbits [54]. Recently, ibutilide-induced QT lengthening has been diminished by oral progesterone in healthy female volunteers in a double-blind, placebo-controlled study [55]. While $I_{Ca,L}$ was decreased by progesterone [32] (namely under cAMP-stimulated conditions [52]), estradiol increased this current (as has been mentioned above [32]). The inhibitory effect of progesterone on $I_{Ca,L}$ is moreover accompanied by its activation effect on the slow component of delayed rectifier potassium current I_{Ks} [32,52] (Fig. 17.3; for details about sex differences in I_{Ks}, see Section Voltage-gated potassium channels). These progesterone effects were shown to be mediated through nongenomic activation of the NO release [52]. The observed variations in cardiac electrophysiology during the menstrual cycle were shown to induce arrhythmogenic substrate in female cardiac cell and tissue models, particularly during the late follicular phase (when the estradiol concentration is maximal) and in the case of drug-induced deceleration of cardiac repolarization, either alone [56,57] (Fig. 17.4) or combined with acute sympathetic arousal [58].

Voltage-gated potassium channels

Many of the cardiac voltage-gated potassium channels show considerable intersex differences, in agreement with the decelerated repolarization process in female in comparison to male. Unfortunately, the available literature data are not, again, fully consistent.

Vicente et al. [59] observed that the shorter QTc in men is due to shorter early repolarization; in contrast, the depolarization and late repolarization were significantly longer in men. As shown by simulations performed by Verkerk et al. [19,34,60], males are more sensitive to impaired balance of depolarizing and repolarizing forces during early phases of AP (i.e., they have reduced depolarization reserve [61]) and, thus, to all-or-none repolarization. This is in agreement with the more prominent notch of AP in male and with higher prevalence of tachyarrhythmias related to the Brugada syndrome in men [61].

Simulations performed by Vicente et al. [59] suggested that the changes of early repolarization were mostly caused by the effect of testosterone on $I_{Ca,L}$ (see Section Voltage-gated calcium channels and Ca^{2+} handling mechanisms). Another current essentially influencing the early repolarization of AP is the transient outward potassium current (I_{to}; formed namely by the Kv4.3 α-subunit and the modulatory KChIP2 subunit in the human heart; Fig. 17.1). Intersex differences of this current were also reported—I_{to} was smaller in female than in male (e.g., in mice [62,63], in the

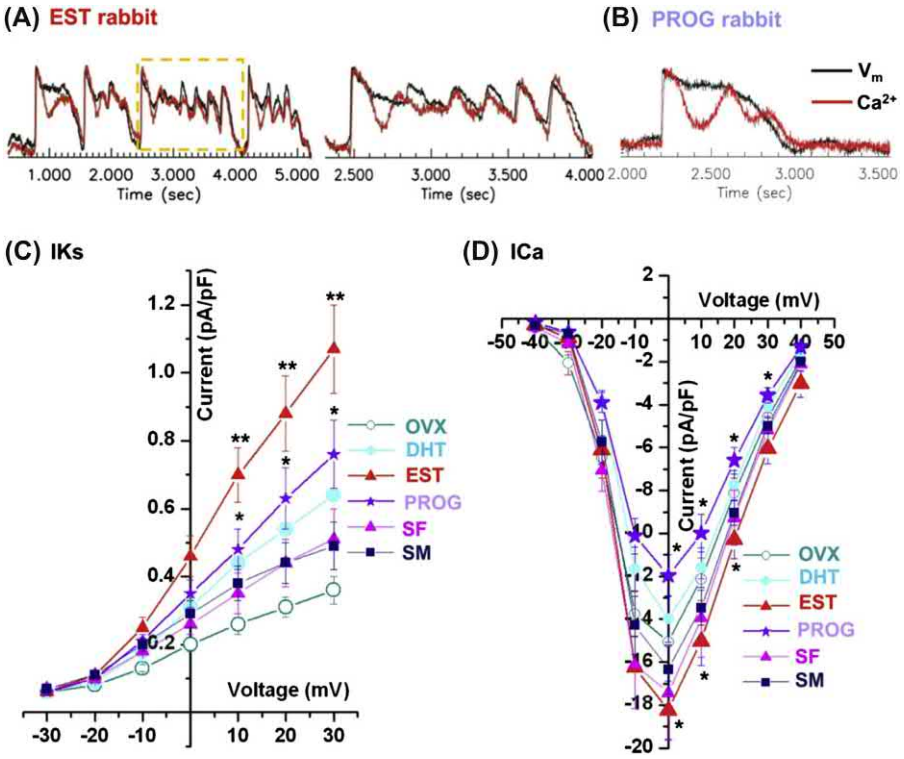

FIGURE 17.3 Effect of 90-day exposure of estradiol (EST) and progesterone (PROG) on the membrane potential (Vm; black lines in A and B), intracellular oscillations of Ca^{2+} concentration (Ca^{2+}; red lines in A and B), slow delayed rectifier current (I_{Ks}; C), and L-type Ca^{2+} current (I_{Ca}; D) in ovariectomized rabbits suffering from long-QT syndrome type 2 (LQT2); *DHT*, rabbits after 90-day treatment with dihydrotestosterone; *OVX*, ovariectomized LQT2 rabbits after 90-day treatment with placebo; *SF*, sham-operated female LQT2 rabbits; *SM*, sham-operated male LQT2 rabbits. *Reproduced with permission from Odening KE, Choi BR, Liu GX, Hartmann K, Ziv O, Chaves L, Schofield L, Centracchio J, Zehender M, Peng X, Brunner M, Koren G. Estradiol promotes sudden cardiac death in transgenic long QT type 2 rabbits while progesterone is protective. Heart Rhythm 2012;9(5):823–32.* https://doi.org/10.1016/j.hrthm.2012.01.009.

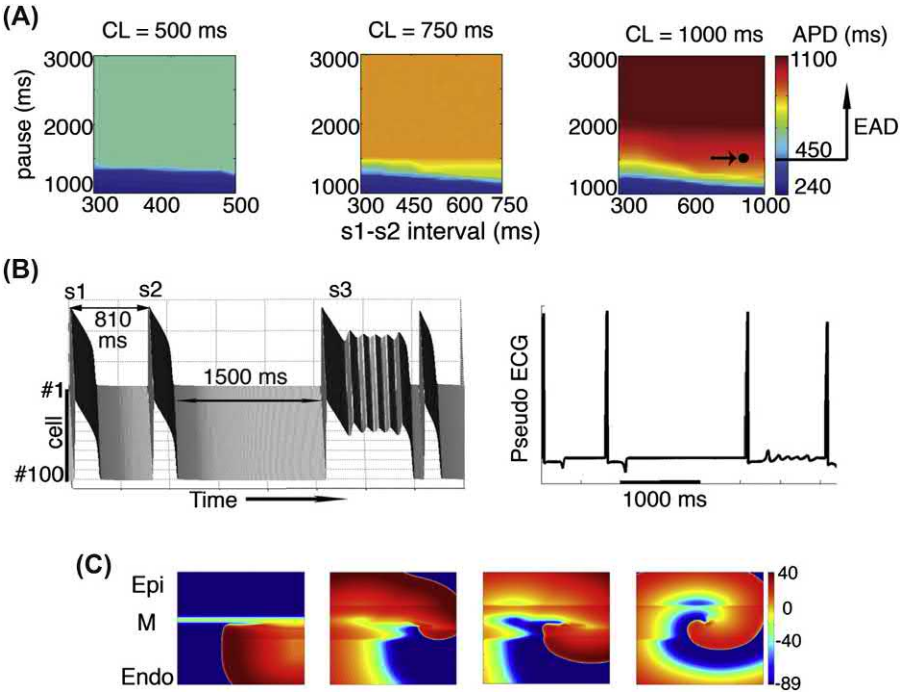

FIGURE 17.4 Simulations showing increased susceptibility to early afterdepolarizations (EADs) and reentry formation during late follicular phase (when the estradiol concentration is maximal, ~1 nM) and consequent drug-induced deceleration of cardiac repolarization (due to presence of 10 nM E4031 causing ~8% inhibition of I_{Kr} alone, but ~33% inhibition of I_{Kr} in the presence of 1 nM estradiol, as shown by Kurokawa et al. [31]). (A) Stimulation of the model cell at the basic cycle length (BCL) of 500, 750, and 1000 ms (s1) was followed by varying s1–s2 intervals (abscissa) and long pause intervals between 1000 and 3000 ms (ordinate). The resulting action potential duration (APD) is indicated by color gradient. Pause above 1500 ms at BCL 1000 ms resulted in formation of severe EADs. The point in the right panel indicates an EAD formed at the pause of 1500 ms and s1–s2 interval of 810 ms at BCL of 1000 ms. (B) Simulation in a coupled one-dimensional cell tissue (100 cells) using the same protocol as in the part A showing EAD formation and pseudo-ECG at the point in the part A, right panel. (C) Simulation in 2D heterogeneous tissue using short-long-short pacing protocol showing reentrant activity; Epi, M, and Endo—subepicardial, midmyocardial, and subendocardial tissue, respectively. *Reproduced with permission from Yang PC, Kurokawa J, Furukawa T, Clancy CE. Acute effects of sex steroid hormones on susceptibility to cardiac arrhythmias: a simulation study. PLoS Comput Biol 2010;6(1):e1000658.* https://doi.org/10.1371/journal.pcbi.1000658.

subendocardium of dog [14], in the human midmyocardium, non-significant change [19]; Fig. 17.2D). It was demonstrated to be related to lower transcriptional levels of Kv4.3 in mice [63]; in ovariectomized mice, Kv4.3 expression was downregulated by estrogen treatment. In contrast, chronic exposure to testosterone increased I_{to} by increasing expression of Kv4.3 in human derived cardiomyocytes [64]. A lower expression of modulatory β-subunit of the I_{to} channel, KChIP2, was reported in the female human cardiac tissue by Gaborit et al. [39]. By the way, KChIP2 expression varies within the ventricular wall of large mammals (human and dog) and forms the well-known transmural gradient of I_{to} in ventricles [65]. A lower expression was also detected for Kv1.4 (i.e., α-subunit contributing to formation of the I_{to} channels) in the female human subendocardium [39].

The ultrarapid delayed rectifier potassium current (I_{Kur}; formed by the Kv1.5 α-subunit and the modulatory Kvβ2 subunit in the human heart, being expressed especially in the atria, Fig. 17.1) was also shown to be lower in female, at least in mice (e.g., Refs. [17,63,66]); downregulation of the Kv1.5 expression in female mice was corresponding with the I_{Kur} measurements. Kv1.5 expression was downregulated by estrogen treatment in ovariectomized mice [63]. In the female human subendocardium, Kv1.5 expression seems to be comparable to men [39].

In contrast, other studies did not demonstrate any sex differences in Kv1.5 and Kv4.3 expression [67,68]. These divergent findings might be caused by use of a different strain of mice, C57BL, at least in the case of data by Brunet et al. [68]. This mice strain was proved to be chronically androgen-deficient [69].

Both the rapid and slow components of delayed rectifier potassium current (I_{Kr} and I_{Ks}, respectively), largely responsible for the final AP repolarization, namely in ventricles (Fig. 17.1), were also reported to be smaller in the female heart. Liu et al. [70,71] demonstrated that I_{Kr} (formed by the Kv11.1, hERG, α-subunit, and maybe also by the modulatory KCNE1 subunit, in the human heart) is significantly lower in the female rabbit ventricle. Acute application of estradiol at a physiological-relevant concentration of 1 nM was reported to suppress I_{Kr} in guinea pig ventricular myocytes in a receptor-independent manner (due to modification of the voltage dependence), causing significant prolongation of APD; lack of testosterone effect was also proved [31]. In agreement, a lower expression of hERG was observed by Gaborit et al. [39] in the female human ventricles. Acute application of testosterone at physiologically relevant concentration modestly (by 13% −15%) increased the endogenous hERG current in human neuroblastoma cells [72]. I_{Ks} (formed by the Kv7.1, KvLQT1, α-subunit, and the modulatory KCNE1 subunit in the human heart) was smaller in female rabbit, and its β-adrenergic activation was weaker [16] (for more data related to blunted β-adrenergic response in female cardiomyocytes, see Section Voltage-gated calcium channels and Ca^{2+} handling mechanisms). James et al. [38] confirmed smaller I_{Ks} in the female guinea pig ventricles. In the human female ventricle, expression of minK was reduced in comparison with males [39]. Acute application of testosterone was reported to increase I_{Ks} at physiologically relevant concentrations; the effect was mediated by an increase of cytosolic concentration of NO [20]. Estradiol was reported to acutely decrease I_{Ks} in guinea pig ventricular myocytes [31]. In contrast, Xiao et al. [14] demonstrated larger I_{Ks} in female canine subendocardial and subepicardial tissues; no differences were apparent in the midmyocardium. Odening et al. [32] observed that, surprisingly, both estradiol and dihydrotestosterone increased I_{Ks} in orchiectomized rabbits after 90-days exposure (estradiol did it even to a higher extent than dihydrotestosterone - Fig. 17.3C). Importantly, progesterone was shown to increase I_{Ks} (Fig. 17.3C) [32,52] through a nongenomic activation of the NO release [52], which decreases proarrhythmic tendency in women during the luteal phase (see Section Voltage-gated calcium channels and Ca^{2+} handling mechanisms) and might explain the differences observed in various studies.

Regarding inward rectifier potassium (shortly Kir) currents, sex differences were also shown. The inward rectifier potassium current (I_{K1}; formed by the Kir2.1, Kir2.2, and Kir2.3 α-subunits in the human heart), an essential ionic membrane current stabilizing the resting membrane potential and contributing to the last segment of final repolarization (Fig. 17.1), was reported to be decreased in female myocardium, both in guinea pigs [38] and in rabbits [70], which is consistent with a reduced expression of Kir2.3 in the female human ventricle [39]. In agreement, chronic exposure to dihydrotestosterone was shown to increase I_{K1} in ventricular myocytes of orchiectomized rabbits [71]. Modulation of I_{K1} by 3-weeks dihydrotestosterone treatment in orchiectomized rabbits was also described by Carnes and Dech [73], however, the peak outward I_{K1} was not affected in this study. Expression of the Kir2.1 subunit, the most abundant subunit forming I_{K1} in ventricles, was comparable in the female and male human ventricle [39]. The ATP-sensitive potassium current ($I_{K(ATP)}$; formed namely by the Kir6.1 and Kir6.2 α-subunits and the regulatory SUR2A subunits in the human heart) seems to be comparable in the male and female rat heart [21]. However, a higher expression of both Kir6.2 and SUR2A and higher $I_{K(ATP)}$ was reported in the guinea pig female ventricles [74]. In contrast, Gaborit et al. [39] observed that both Kir6.2 and SUR2 were less expressed in the female healthy human ventricles in comparison with the male ones, whereas Kir6.1 was comparable in the male and female tissue. It is a question if these substantially different data are only due to interspecies differences. In the case of

acetylcholine-sensitive potassium current ($I_{K(Ach)}$; formed by the Kir3.1 and Kir3.4 α-subunits), expression of the Kir3.4 subunit did not show sex differences in the human ventricular samples [39]. Other data are not available.

Other subtypes of potassium channels

Other subtypes of potassium channels may also show sex differences. Recently, sex-specific activation of the potassium channels conducting apamin-sensitive small conductance Ca^{2+}-activated (SK) current has been revealed [75]. These authors have shown that the current is abundantly activated during application of isoproterenol in the female rabbit ventricle. Electromechanically discordant phase 2 repolarization alternans and even ventricular fibrillation were induced.

Other cardiac ionic channels and transporters

Gaborit et al. [39] reported an isoform switch in sodium/potassium-ATPase (Na^+/K^+-ATPase) in the female ventricular tissue samples, expressing more α1- and less α3-subunit than the male hearts. They also showed that connexin 43 was less expressed in the female ventricle. Opposite finding, i.e., significantly higher expression levels of both mRNA and protein in female, was reported by Stauffer et al. [76] in the rat heart. In agreement, estradiol was demonstrated to increase expression of connexin 43 in rat neonatal cardiomyocytes [6].

No sex differences were observed in expression of various subunits forming chlorine channels in the human ventricle [39]. No sex differences were also found in expression of the hyperpolarization-activated (funny, I_f) channel in the human atrial samples [77] and in the human ventricular tissue [39]. Other data describing sex-related differences in cardiac ionic channels and transporters have not been found in the available literature.

Conclusions

Sex differences may be found in many basic cardiac ionic membrane currents. These differences are mostly subtle. Complex of changes in multiple currents is therefore likely needed to result in macroscopic differences of the cardiac electrophysiology observed between male and female.

The most pronounced differences in the ventricular tissue have been observed in $I_{Ca,L}$ and various repolarizing potassium currents, namely I_{to}, I_{Kr}, I_{Ks}, and I_{K1} (as was extensively reviewed in the Sections Voltage-gated calcium channels and Ca^{2+} handling mechanisms and Voltage-gated potassium channels). In the female myocardium, $I_{Ca,L}$ was shown to be higher, whereas potassium currents were reported to be lower in the published studies using various animal species including human. These differences

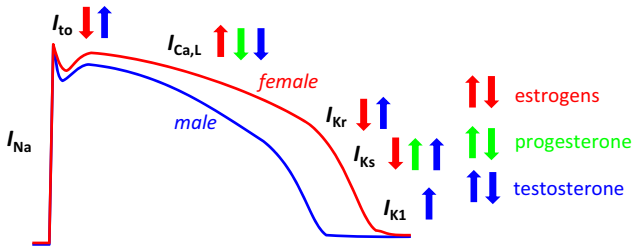

FIGURE 17.5 Schematic overview of changes of pivotal ionic membrane currents in ventricular cardiomyocytes under the effect of estrogens, progesterone, and testosterone (only changes reported consistently in the available literature are included). For details, please see the text.

result from opposing effects of testosterone and estrogens on $I_{Ca,L}$ and potassium currents (Fig. 17.5). Progesterone seems to accelerate repolarization similarly as testosterone, which causes variations of the cardiac repolarization and susceptibility to arrhythmias observed in women during menstrual cycle. These observations may roughly explain most of the sex-related specificities in the cardiac cellular electrophysiology, as was suggested by studies dealing with mathematical modeling of sex differences (e.g., Refs. [19,34,56,60,78]). Formation of arrhythmogenic substrate was suggested by both cell and tissue modeling in female myocardium, particularly during the late follicular phase and drug-induced deceleration of cardiac repolarization, either alone [56,57] or combined with acute sympathetic arousal [58].

Beside the genomic pathways mediating chronic effects of sexual hormones (e.g., estradiol on $I_{Ca,L}$ and I_{NaCa} [4,25,26,29,30,40]), the nongenomic ones may also contribute to the sex differences in cardiac electrophysiology and cause acute effects of sexual hormones on the cardiac ionic channels. They are represented either by a direct action of sexual hormones on the channels (e.g., estradiol on I_{Kr} [31]) or by an indirect modification of the channel function, for example, through activation of NO synthase (e.g., progesterone on I_{Ks} [52] and testosterone on I_{Ks} and $I_{Ca,L}$ [20]).

Unfortunately, the available literature data are often inconsistent, showing conflicting results. It likely results from varying experimental conditions, including various species used for the analyses and inclusion of the female cardiac tissue at various stages of the menstrual cycle (usually even not mentioned in the studies). Future studies should respect fluctuations of cardiac electrophysiological parameters in the female myocardium during the cycle.

In some cases, data are few or even missing, which disables final conclusion regarding the observed sex-related differences. It applies to individual ionic membrane currents and also to the atrial tissue in total. Only few data focused on the sex differences in the atrial tissue are available [10,24,77], though a higher incidence and prevalence of the atrial fibrillation (AF) was documented in men

of the same age, and in contrast, women with AF were demonstrated to be more symptomatic, to present with more atypical symptoms, and to show lower responsiveness to the antiarrhythmic therapy [79].

Testosterone was suggested to play a protective role against arrhythmias related to prolonged QTc interval, including its drug-induced prolongation. Progesterone seems to show similar protective effect in women. It is mostly apparent during the luteal phase of the menstrual cycle, when the progesterone concentration steeply increases and the progesterone protective effects may therefore overwhelm the estrogen proarrhythmic effects. All these facts should be taken into account in the case of safety pharmacology testing to select (or develop) the most reliable models, as was deeply discussed by Jonsson et al. [61].

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Chapter 18

Development of electrocardiographic sex differences during puberty

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It is well known that sex differences of electrocardiographic values exist in adult population. The most significant differences are expressed in a repolarization phase of heart cycle that corresponds to QT interval on surface electrocardiogram (ECG). The QT interval duration reflects the overall duration of action potentials across ventricular myocardium. Both abnormal QT prolongation and shortening are a result of abnormal ventricular electrophysiology, which may lead to an increased risk of arrhythmias and/or sudden cardiac death (SCD). Abnormalities of the QT interval are most pronounced in patients with hereditary channelopathies—congenital long QT syndrome (LQTS) and short QT syndrome (SQTS). Compared with SQTS, the population prevalence of LQTS is more frequent by two to three magnitudes. LQTS individuals present with a prolonged QT interval duration, which increases the risk of a specific ventricular tachycardia "Torsade des Pointes," which, in turn, may lead to SCD.

Congenital LQTS was initially considered to be very rare, ranging from 1:20,000 [1] to 1:10,000 [2], but its prevalence has now been confirmed around 1:2500 [3]. It is the most often diagnosed inherited arrhythmic syndrome. Obviously, the earlier the diagnosis, the greater the chance of successfully avoiding potentially fatal complications. Thus, establishing normal values of the QT interval in children is of substantial importance.

Cardiac repolarization is a dynamic process, and its duration depends on the heart rate (HR). QT interval shortens with increasing HR and vice versa. This dynamic behavior, called the QT/RR relationship, is known to be different between different subjects [4]. Therefore, the usually used adult cutoff values of QT interval prolongation ($>$460 and $>$ 440 ms in adult females and males, respectively) depend on the underlying HR and application of HR correction formula and are thus truly valid only at HR of 60 beats per minute (bpm). Nevertheless, in adults, general correction formulae, such as the Fridericia formula, do not lead to very substantial errors of assessment, unless the underlying HR is very different from 60 bpm.

In children, the situation is much more problematic and complex. In preadolescent children, QT interval duration is the same in both sexes. It is not well known when the sex-related changes evolve during adolescence, whether QT prolongs in females or shortens in males, and to which extent are these differences also influenced by the differences in resting HR that also appear during puberty. Presently, normality limits for children have only been suggested in studies that were either small or used unreliable automatic QT measurement [5–9]. A large Japanese study recently attempted to establish the normal QT limits for children [10]. ECGs were recorded in approximately 4000 children at the age of 6, 12, and 15 years. In this study, some sex-related differences were present already among 12-year-old participants. The results from this Japanese study are little bit at odds with another study [11]. The American authors retrospectively collected ECG from 1275 boys and 1125 girls (age 1 month to 18 years) of different ethnicity (almost 920 white children, 750 black and 790 other or mixed children). They also divided children to 36 groups according to sex, race, and age (less than 3 years, 3–6, 6–12, 12–16, and 16–18 years). QT interval was corrected to HR using both Bazett and Fridericia formulas. The sex-related differences were present in children more than 3 years old especially in children at the age of 3–6 years and 16–18 years. In the other groups, the differences were less significant. In the third study in Taiwan, authors performed a population study consisting of 898 schoolchildren and adolescents at the age of 6–18 years during the period of 2003–05 [12]. About 69 rest ECG parameters were studied comparing

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boys with girls in each of three age groups (6−9, 9−13, and 13−18 years). The significant QTc sex differences were observed in the 13−18 years age group. The mean QTc duration was 401 ± 24.71 ms for boys and 413 ± 20.39 ms for girls ($P < .01$).

Nevertheless, all these studies suffered from severe limitations: QT interval was evaluated only from short ECG recordings, thus omitting the effects of the so-called QT/RR hysteresis [13], which, considering the substantial HR variability in children, is bound to lead to substantial inaccuracy. The Japanese study also performed the measurements only in ECG paper prints, leading to clear measurement imprecisions (obvious from the published illustrations). The results of the American study may have been biased because of not blinded results of automatic waveform interval and amplitude measurements to pediatrics cardiologist who reviewed the ECG. In any of these works, the authors did not collect any information about children and their concomitant medications, which can significantly affect the duration of QT interval. Both Japanese and American studies relied on Fridericia and Bazett formula, which is unlikely to reflect valid QT/RR relationship in children.

Previous studies about relationship between QT duration and underlying HR showed the subject-specific substantial differences between different individuals [4]. Also, generic HR corrections, such as Bazett, Fridericia, or Framingham formulae, can be inaccurate if these are applied to QT intervals measured at HR well distant from 60 bpm [14]. The HR and hysteresis correction of the QT interval in children is a specific problem. Because of elevated HR, ECG recordings in children are frequently considerably remote from 60 bpm, making the diagnoses of QT abnormalities dependent on the accuracy of rate correction. At the same time, however, the development of QT/RR relationship during childhood and adolescence is not known, and it can only be speculated that different corrections are needed at different ages. Moreover, since the QT/RR relationship shows interindividual differences, pooling population data might lead to large imprecisions [15]. Appropriate age- and sex-related HR corrections can only be derived as averages of QT/RR curvatures and slopes of individuals rather than as the QT/RR curvature and slope of pooled single measurements in different individuals since, for simple mathematic reasons, these can be very different, thus leading to erroneous conclusions.

To solve this unmet physiologic and clinical need, a new investigation was performed, providing sufficient spectrum of QT/RR measurements obtained at broad HR range in healthy children of school age and adolescent uniform age distribution among the ages of 4−19 years in both sexes [16]. The study also contained collection of demographics, health status data, and presence of secondary sex characteristics, which were classified according to recognized standards [17−19]. Every child or adolescent who agreed with this study was investigated. Nevertheless, the ECGs from participants with cardiac abnormality or using hormonal contraceptives or repolarization affecting drugs [20] were excluded before the date analyses.

To increase the HR spread available for QT measurements, investigated children underwent series of postural autonomic provocation maneuvers (simultaneously in small groups). The testing was performed within the premises of the participating school in the midmorning hours. The provocative protocol consisted of seven postural phases each of 10-min duration: supine → sitting → standing → supine → standing → sitting → supine, while postural changes were achieved in no more than 10 s. During supine positions, the children were lying relaxed on their backs on mattresses, with their legs stretched out, not crossed, and their hands along the body. The sitting position was performed on a bench with the back upright without any back support, knees bent at right angles and hands loosely placed in the lap. During the standing position, the children were standing upright with hands alongside the body. During the investigation, younger children listened to nonexciting age-appropriate stories, and others were investigated in quiet noise-free environment.

Each 12-lead recording was divided into 10-s segments with 5-s overlaps between neighboring segments (to avoid missing beats split between two segments). In each segment, representative beats were constructed by superimposing individual P-QRS-T complexes and calculating sample-by-sample voltage medians in each lead. Previously developed software was used to measure P-QRS-T delineations and to obtain automatic QT interval measurements in the representative beat of each ECG segment and to classify the representative beats of segments of each recording into classes of mutually corresponding morphology (separately for the morphology of P waves, QRS complexes, and T waves) [21−23]. Representative image of each morphological class was visually validated; the measurements were performed on computer screen using previously developed measurement software.

Being aware that the QT interval duration depends rather more on the underlying HR than on the rate of the immediately preceding heartbeat cycle [24], we investigated individual QT/RR patterns in each study participant including the curvilinear regression of the relationship. The QT/RR patterns were combined with subject-specific assessment of the QT/RR hysteresis profiles [13]. Using averaging of individually corrected QT values of all measurements available in the given study subject, the so-called QTcI interval was established.

In total, 555 subjects (295 female and 260 male) were enrolled and investigated. The analysis was completed in 268 females and 259 males, and the others were excluded

because of potentially interfering drug therapy, cardiac structural congenital diseases, and one sex-transversal procedure. One subject was excluded because of technical problem. The characteristics of investigated children divided in 13 age-dependent groups are shown in Table 18.1.

The ECG data reported are based on 642,003 measurements of the QT interval and of its 5-min RR interval history. On average, 1218 measurements were evaluated in each included child.

By implementation of QT/RR hysteresis, more tight relationship between the measured QT intervals and the underlying HR was achieved. Fig. 18.1 shows the spread of the QT data around the curvature of the relationship composed by incorporation of QT/RR hysteresis. With this methodology, the curvilinear QT/RR regression residuals were 4.59 ± 2.60 ms in females and 3.87 ± 1.16 ms in males. However, using the RR intervals averaged from the 10-s ECG segments or averages of three RR intervals, these residuals increased to 7.05 ± 2.40 ms in females and 6.73 ± 1.64 ms in males, respectively, to 9.34 ± 2.56 ms and 9.04 ± 1.97 ms ($P < .001$ for all). This phenomenon was detected in every study participant (Fig. 18.2). With increasing age, QT/RR regression residuals increased, and it was statistically significantly different in both females and males ($P < .01$) (see in Fig. 18.3). The extent of the QT/RR hysteresis is standardly expressed by its time constant defined as the time interval required for 95% of the adaptation of QT interval to occur after an HR change. Furthermore, Fig. 18.4 shows that the extent of the QT/RR hysteresis is not dependent of age and is very close to the constant of 2 min.

As shown in previous studies [12,25], HR variability was also age dependent in our study. Younger children had both the slowest and also the fastest HRs higher than the adolescents. The decrease of minimum and maximum HRs was statistically significant ($P < .0001$ respectively $< .001$). This age dependency of the fastest and the slowest HRs and HR range are shown in Fig. 18.5. The bottom graph also shows that the HR spreads of QT/RR patterns were substantial in all study subjects. In that way, the individual QT/RR patterns were accurately defined.

One of the principal results of this study compared QTcI to age in girls and boys. Fig. 18.6 shows the significant QTcI prolongation dependency on age in females (0.70 ms per year, $P = .02$) and significant shortening of QTcI with advancing age in males (0.64 ms per year, $P = .03$). The relationship between QTcI and age is nonlinear (see the middle panel of Fig. 18.6). Until the 12 age, the values of QTcI are not different in both sexes. Approximately from 13 years of age, the QTcI interval started to decrease with dependency on presentation of secondary sex signs in males. In females, another pattern of development was seen. On the contrary to the assumptions, in females, the QTcI changes only at the age of approximately 16 years and was not dependent on presentation of secondary sex signs. From the age of 18 years, the highest difference of average QTcI between females and males—24.1 ms—was detected.

TABLE 18.1 Investigated population.

	Female				Male			
Age [years]	N	Sign	Height [cm]	Weight [kg]	N	Sign	Height [cm]	Weight [kg]
≤7	17	0	115.7 ± 5.2	20.5 ± 2.8	15	0	119.1 ± 6.9	24.7 ± 7.4
7–8	14	1	128.1 ± 9.8	26.1 ± 3.9	14	0	128.5 ± 6.0	25.9 ± 3.5
8–9	23	1	132.5 ± 5.4	28.4 ± 4.1	18	0	135.4 ± 5.7	31.9 ± 5.6
9–10	15	5	139.2 ± 7.0	33.7 ± 6.3	11	0	141.9 ± 7.8	36.1 ± 8.6
10–11	23	7	144.2 ± 5.6	36.5 ± 5.6	24	1	145.0 ± 7.1	38.0 ± 8.1
11–12	15	12	149.9 ± 7.8	38.4 ± 7.5	24	9	150.3 ± 6.9	44.6 ± 9.7
12–13	22	18	159.1 ± 5.6	48.3 ± 10.3	29	20	160.6 ± 10	52.9 ± 12.5
13–14	23	22	160.8 ± 8.0	48.2 ± 6.1	20	16	163.5 ± 6.6	49.6 ± 9.2
14–15	22	22	166.2 ± 5.2	58.3 ± 12.7	16	13	173.7 ± 7.3	59.9 ± 10.7
15–16	34	34	165.8 ± 5.3	56.7 ± 7.5	33	31	177.8 ± 6.9	68.1 ± 9.7
16–17	28	28	167.6 ± 5.4	58.3 ± 6.7	20	20	180.0 ± 7.7	72.7 ± 8.6
17–18	11	11	173.5 ± 4.6	64.3 ± 12.6	16	16	182.2 ± 6.4	70.6 ± 9.2
>18	21	21	165.9 ± 7.3	57.0 ± 8.3	19	19	178.5 ± 6.5	70.4 ± 11.9

N, number of subjects; *Sign*, number of children with secondary sex signs.

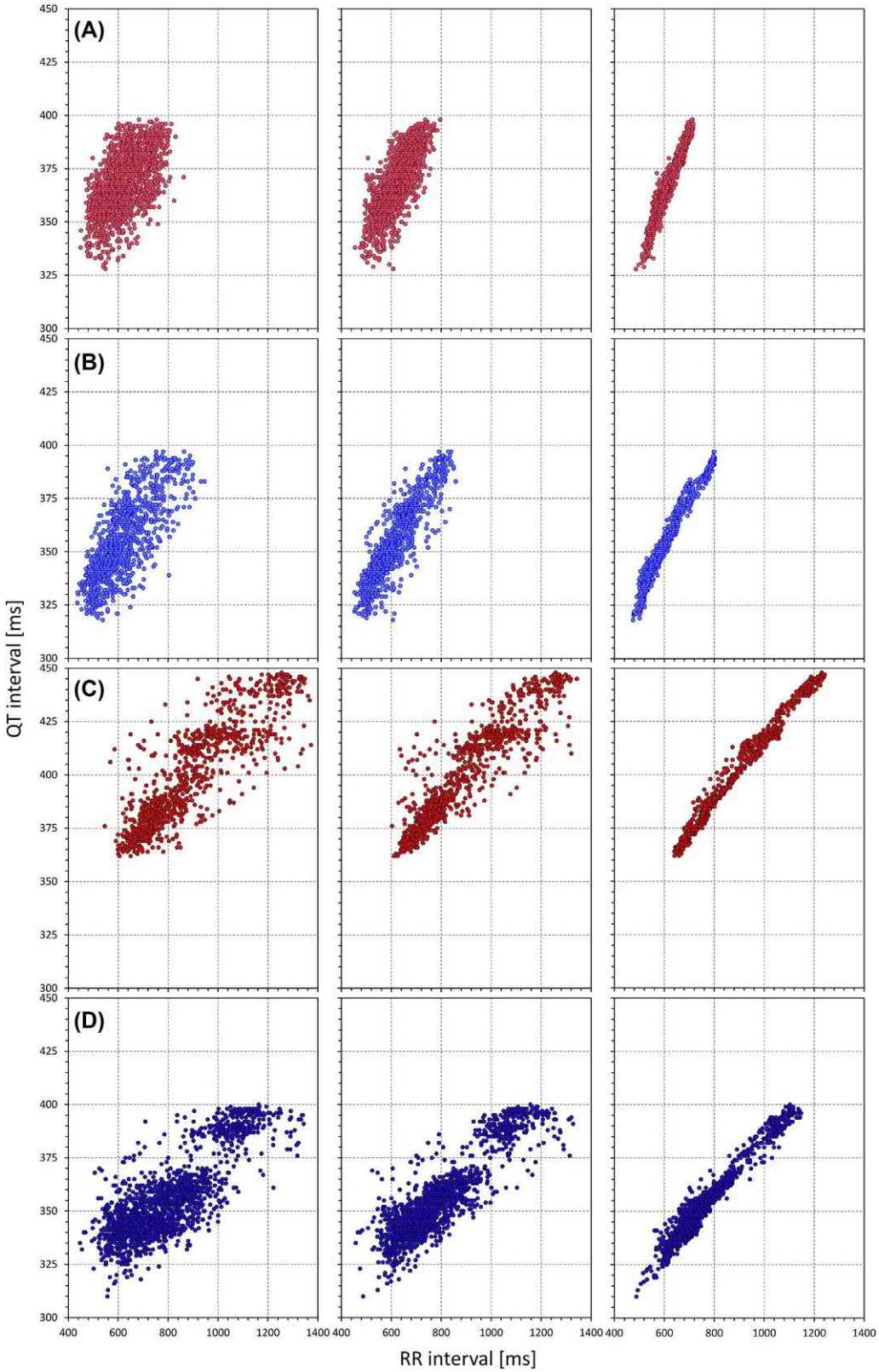

FIGURE 18.1 Examples of comparisons of QT/RR relationship using different RR interval expressions. Each row of panels corresponds to one subject. In each subject, the QT interval measurements are the same, but the panels on the left relate the QT intervals to the averages of three RR intervals, the panels in the middle to 10-s RR interval averages, and the panels of the right to the RR interval values obtained from the 5-min histories of the QT interval measurements by individual QT/RR hysteresis profiles. Note the increase of the regression fit from the left panels to the right panels. Cases A, B, C, and D correspond to a female aged 7.4 years, a male aged 7.7 years, a female aged 18.7 years, and a male aged 18.7 years, respectively. *Reproduced with permission from Andrsova I, Hnatkova K, Helanova K, Sisakova M, Novotny T, Kala P, et al. Individually rate corrected QTc intervals in children and adolescents. Front Physiol 2019;10:994. https://doi.org/10.3389/fphys.2019.00994.*

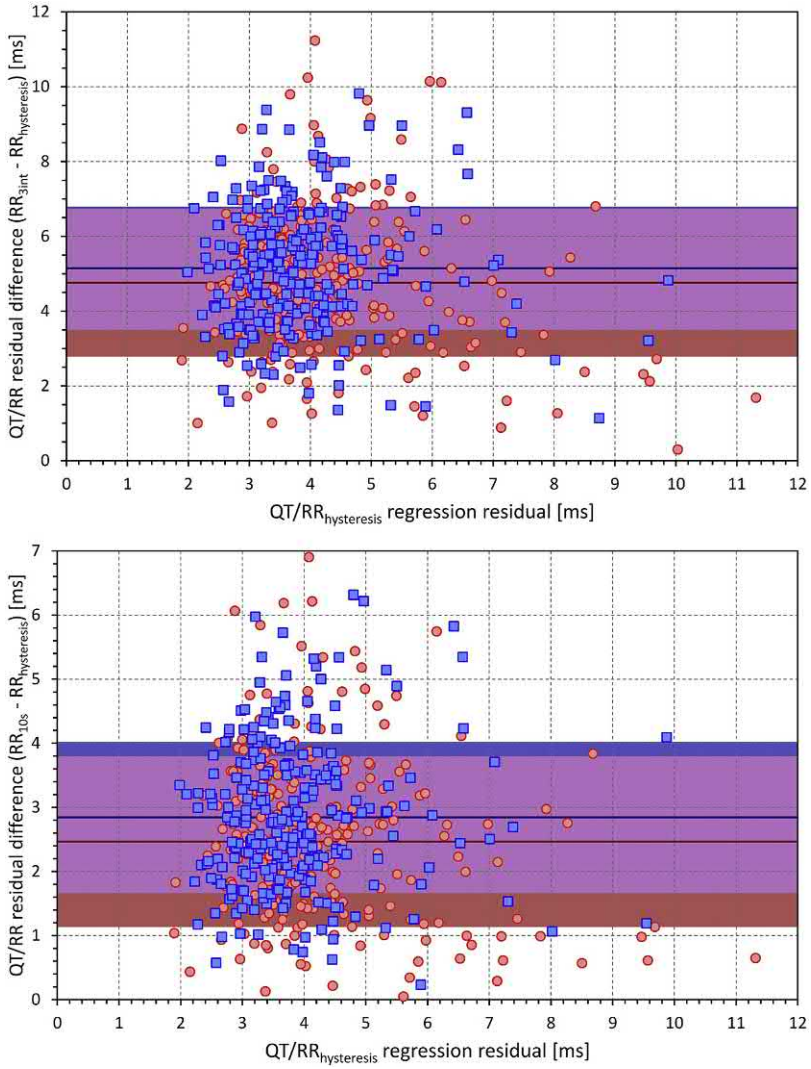

FIGURE 18.2 Scatter diagrams between the curvilinear QT/RR regression residuals involving QT/RR hysteresis correction (horizontal axes) and the increases in the residuals when using three RR interval averages (top panel) and 10-s RR interval averages (bottom panel) instead of QT/RR hysteresis correction. *Red circles* and *blue squares* correspond to female and male subjects, respectively. *Dark red and dark blue lines* are means of the residual increase in females and males, respectively. The *light red and light blue bands* show the intervals of mean ± standard deviation of the sex-specific residual increases. The *violet bands* are the overlaps between the standard deviation bands of both sexes. *Reproduced with permission from Andrsova I, Hnatkova K, Helanova K, Sisakova M, Novotny T, Kala P, et al. Individually rate corrected QTc intervals in children and adolescents. Front Physiol 2019;10:994. https://doi.org/10.3389/fphys.2019.00994.*

The prolongation of QTcI according to age in females was independent of occurrence of secondary sex signs (bottom panel of Fig. 18.6) opposite to males. The comparison between subjects with and without secondary sex signs was statistically significant only in males ($P = .016$); in females, no statistical significant differences were found ($P = .181$). The sex difference between females and males showing the secondary sex signs was highly significant ($P < .001$).

The investigated subjects were dichotomized according to age into the following groups: those older and younger than 10, 11, 12, … 16 years. In males, the QTcI difference between older and younger individuals became apparent at the dichotomy of 13 years ($P = .001$) and remained significant in dichotomies of 14, 15, and 16 years ($P < .001$). Different pattern was observed in females. The QTcI values were similar in all dichotomies of 10−15 years. The significant difference occurred only at the dichotomy of 16 years ($P = .014$).

The curvilinear regressions lead to smaller QT/RR residuals than both linear and log-linear regressions, thus better describing the relationship of QT and RR. In both females and males, difference in QT/RR residuals was smaller in curvilinear model compared with linear one (0.16 ± 0.30 and 0.12 ± 0.24 ms in females and males, $P < .001$) than when comparing curvilinear to log-linear

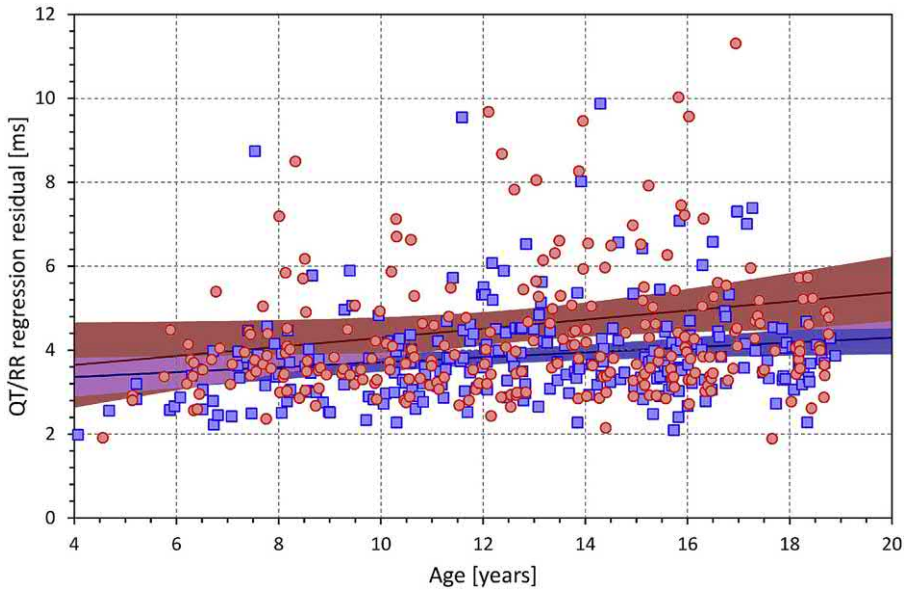

FIGURE 18.3 Age dependency of the curvilinear QT/RR regression residuals. The *red circles* and *blue squares* correspond to the female and male subjects, respectively. The *dark red and dark blue lines* are linear regressions in females and males, respectively; the light red and light blue areas are the 95% confidence bands of the sex-specific linear regression lines. The violet areas are the overlaps between the confidence bands of the regression lines of both sexes. *Reproduced with permission from Andrsova I, Hnatkova K, Helanova K, Sisakova M, Novotny T, Kala P, et al. Individually rate corrected QTc intervals in children and adolescents. Front Physiol 2019;10:994. https://doi.org/10.3389/fphys.2019.00994.*

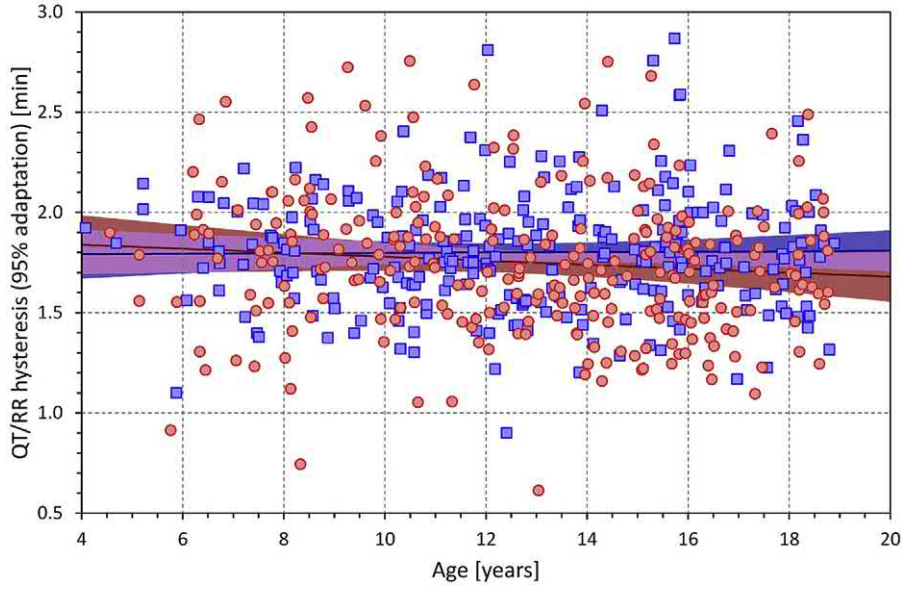

FIGURE 18.4 Age dependency of the intrasubject QT/RR hysteresis time constants (i.e., time intervals needed for 95% adaptation of QT interval duration after heart rate change). The layout and symbol definition are the same as in Fig. 18.3. *Reproduced with permission from Andrsova I, Hnatkova K, Helanova K, Sisakova M, Novotny T, Kala P, et al. Individually rate corrected QTc intervals in children and adolescents. Front Physiol 2019;10:994. https://doi.org/10.3389/fphys.2019.00994.*

models (0.89 ± 0.63 and 0.65 ± 0.30 ms in females and males, $P < .001$). The increases of the residuals from the curvilinear models were also significantly smaller in males compared with females ($P = .02$ for linear models, $P < .001$ for log-linear models). The linear models describe the individual QT/RR relationship better than the log-linear models and thus were used for analysis of age dependency. The results are summarized in Fig. 18.7. In both sexes with advancing age, the QT/RR patterns became gradually shallower, whereas the age effect occurred approximately 13 years onward and was nonlinear (the middle panel of Fig. 18.7). The bottom panel of Fig. 18.7 shows sex-specific

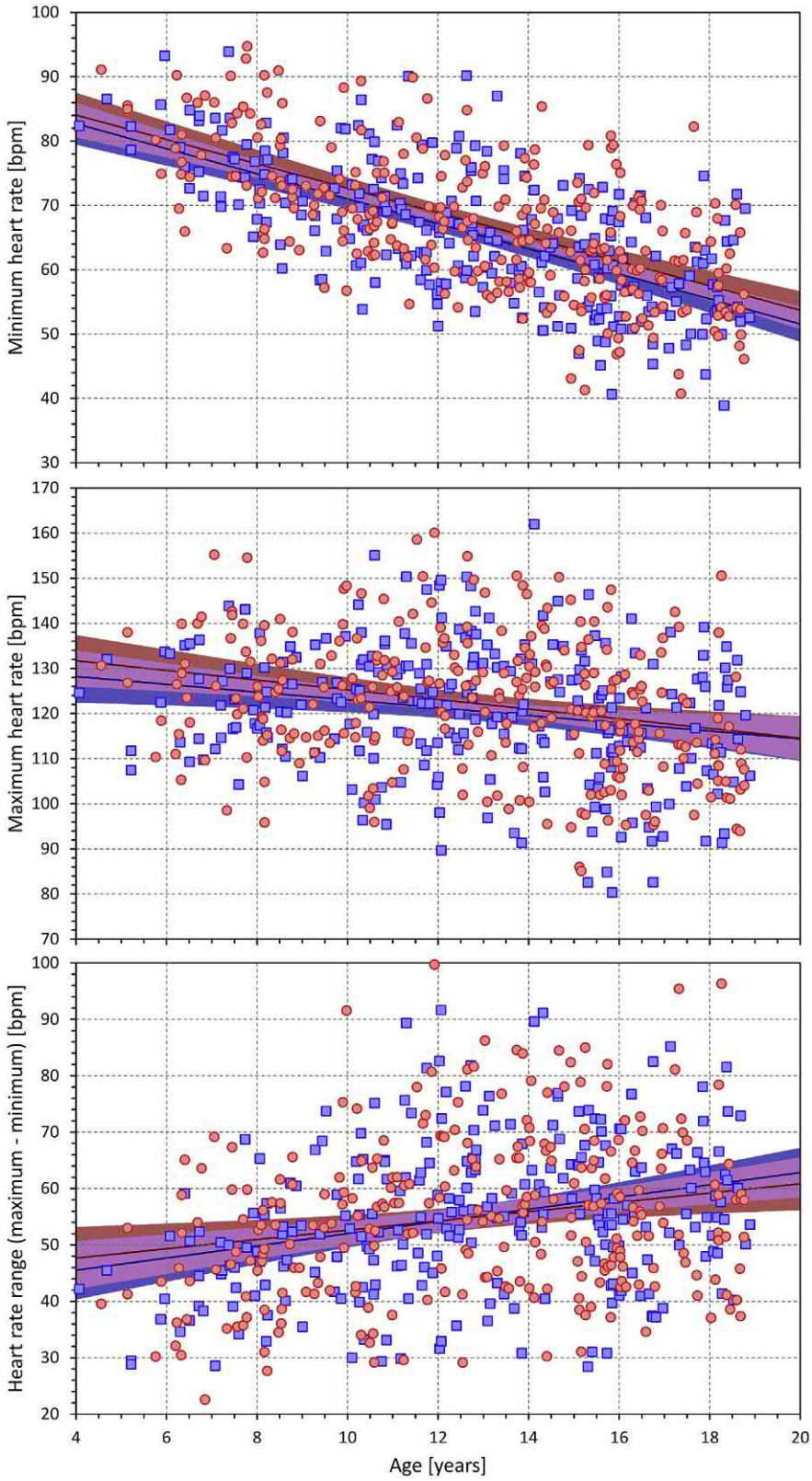

FIGURE 18.5 Scatter diagrams between the age and minimum heart rate (top panel) and maximum heart rate (middle panel), and the range between the minimum and maximum heart rates (bottom panel). The layout and symbol definition in each panel are the same as in Fig. 18.3. *Reproduced with permission from Andrsova I, Hnatkova K, Helanova K, Sisakova M, Novotny T, Kala P, et al. Individually rate corrected QTc intervals in children and adolescents. Front Physiol 2019;10:994. https://doi.org/10.3389/fphys.2019.00994.*

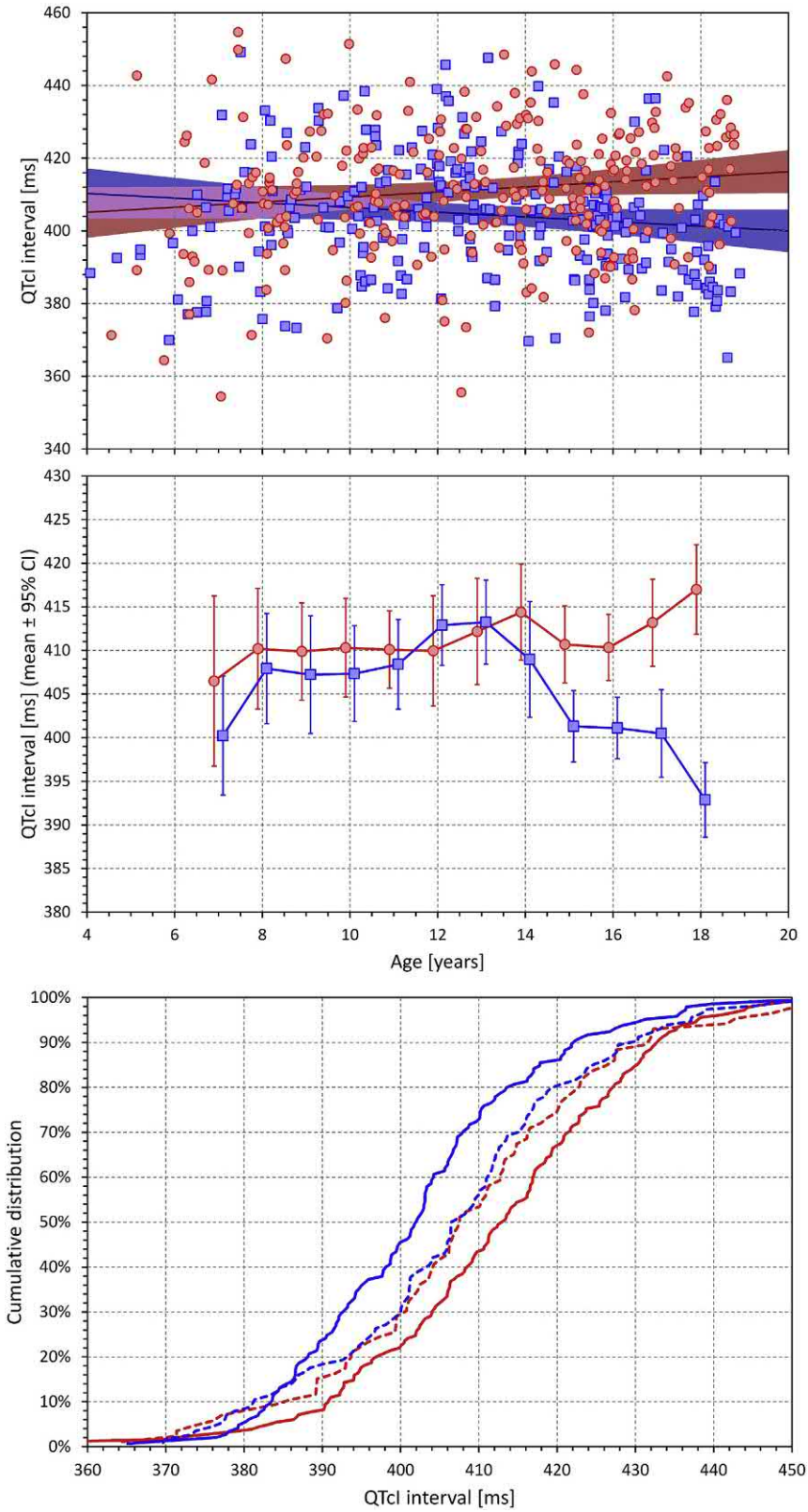

FIGURE 18.6 The top panel shows the scatter diagram between age and QTcI interval (see the legend of Fig. 18.2 for symbol explanations). The middle panel shows the averages of QTcI intervals in age bands <8 years, 7−9 years, 8−10 years, etc. up to 16−18 years and >17 years (each shown approximately at the middle age of the band). The error bars are the corresponding standard deviations. The *red and blue marks* correspond to the females and males, respectively. The bottom panel shows the cumulative distributions of QTcI intervals in subjects without (*dashed lines*) and with (*full lines*) secondary sex signs. The *red and blue lines* again correspond to females and males, respectively. *Reproduced with permission from Andrsova I, Hnatkova K, Helanova K, Sisakova M, Novotny T, Kala P, et al. Individually rate corrected QTc intervals in children and adolescents. Front Physiol 2019;10:994. https://doi.org/10.3389/fphys.2019.00994.*

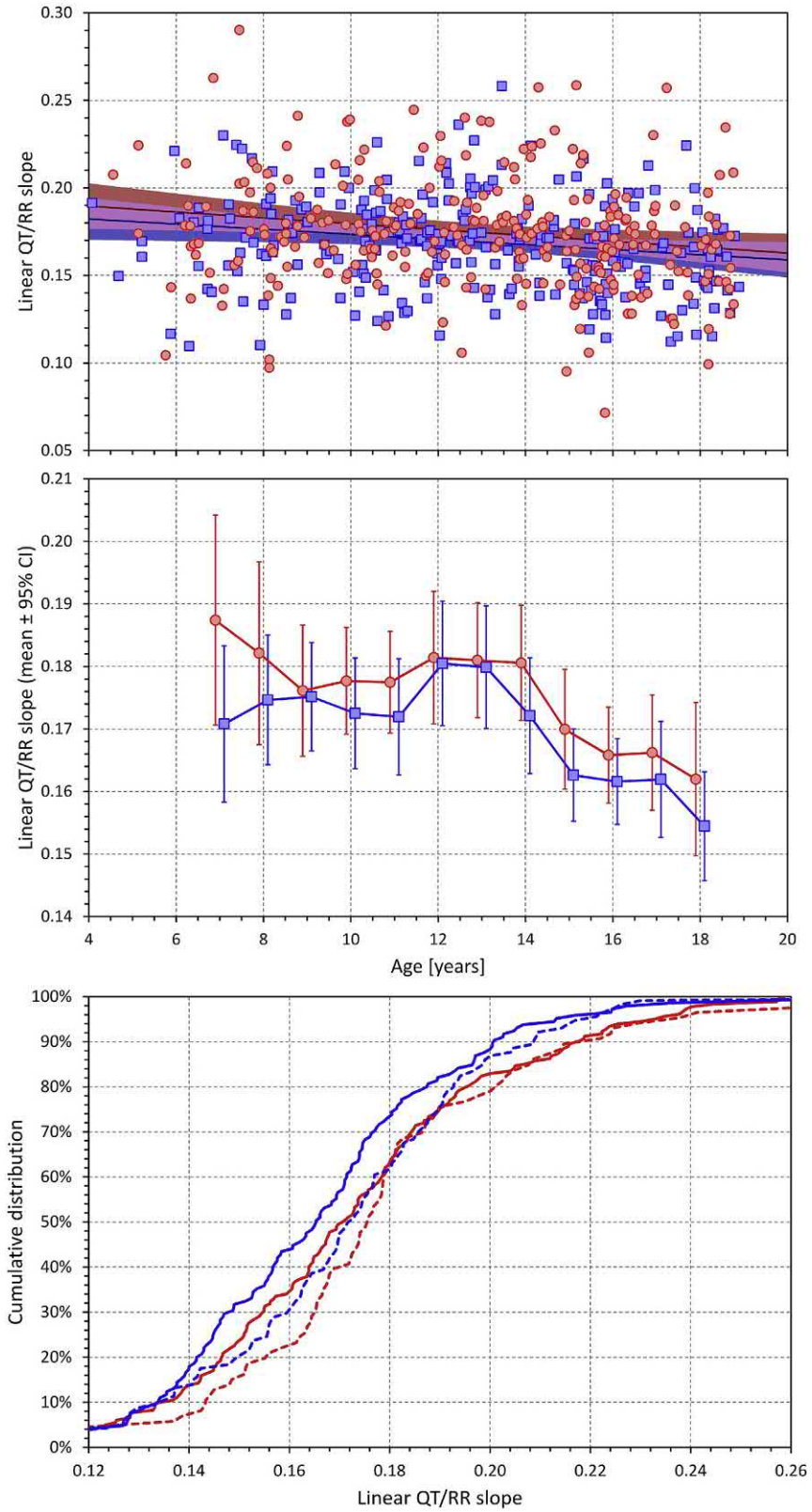

FIGURE 18.7 Development of the age dependency of linear QT/RR slopes in both sexes. The layout and meaning of the three panels are the same as the layout and meaning of the three panels of Fig. 18.3. *Reproduced with permission from Andrsova I, Hnatkova K, Helanova K, Sisakova M, Novotny T, Kala P, et al. Individually rate corrected QTc intervals in children and adolescents. Front Physiol 2019;10:994. https://doi.org/10.3389/fphys.2019.00994.*

trends of shallower QT/RR slopes according to secondary sex signs in males compared with females, but these trends were not statistically significant.

Corresponding analysis of the log-linear slopes is shown in Fig. 18.8. This shows that the log-linear slopes led to erratic results, probably caused by the significantly lesser precision of the log-linear analysis.

This study shows that the sex changes of QTc values during puberty arise like a combination of both prolongation in females and shortening in males during the early adolescent years. However, while we expected clear relationship between occurrence of secondary sex signs and QTc changes in both sexes, other was found (Fig. 18.9). Statistically, significant QTc prolongation occurred 3 years later in females, but the shortening of QTc started directly with occurrence of secondary sex signs in males. More specific results could be achieved by long-term observation of pubertal conditioning, prolonged adaptation to menstruation blood loss, or central and autonomic regulation changes.

We also recognized that wide HR spans known in clinical studies during simple postural maneuvering in adults occurred in relatively young children too. This is very important for judging borderline cases of QTc interval abnormalities in childhood including studying the individual-specific QT/RR profiles.

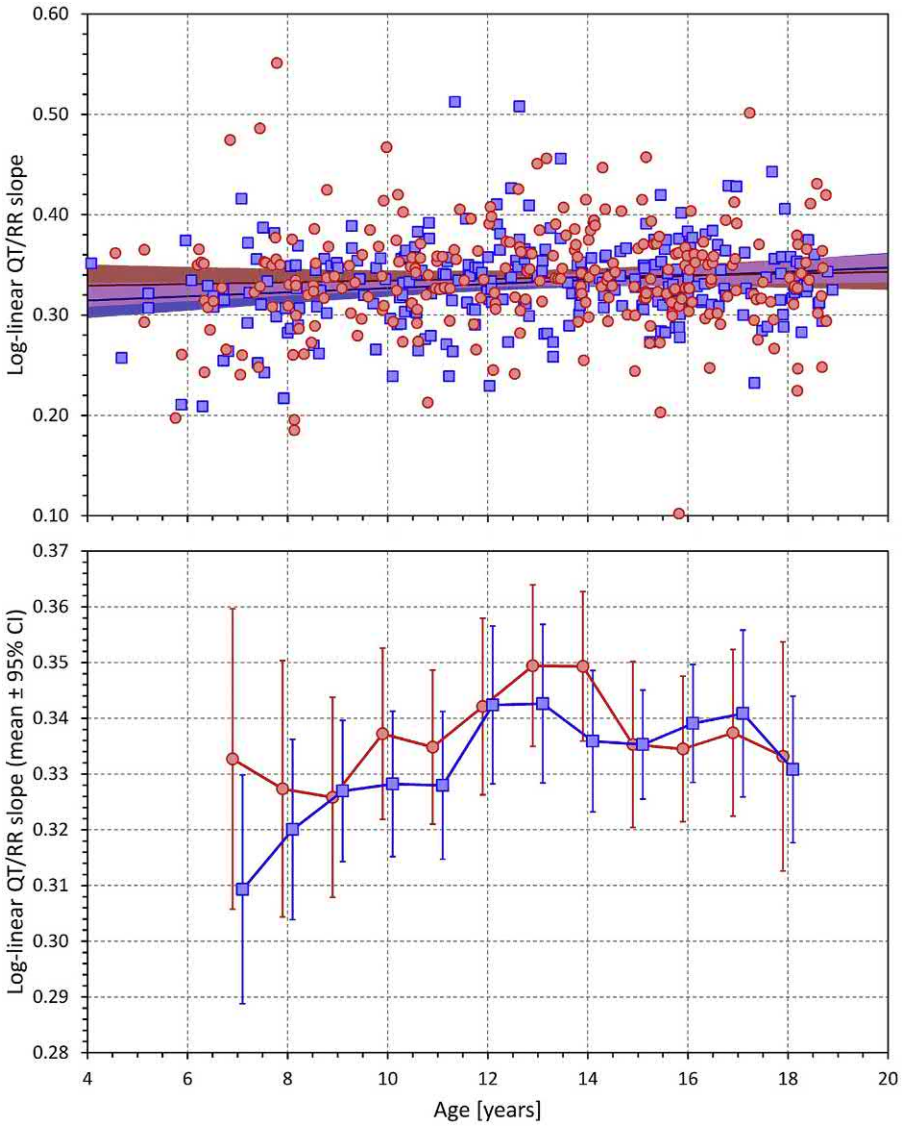

FIGURE 18.8 Age dependency of the slopes of the log-linear QT/RR regressions. The layout of the panels is the same as of the top two panels of Fig. 18.6. *Reproduced with permission from Andrsova I, Hnatkova K, Helanova K, Sisakova M, Novotny T, Kala P, et al. Individually rate corrected QTc intervals in children and adolescents. Front Physiol 2019;10:994. https://doi.org/10.3389/fphys.2019.00994.*

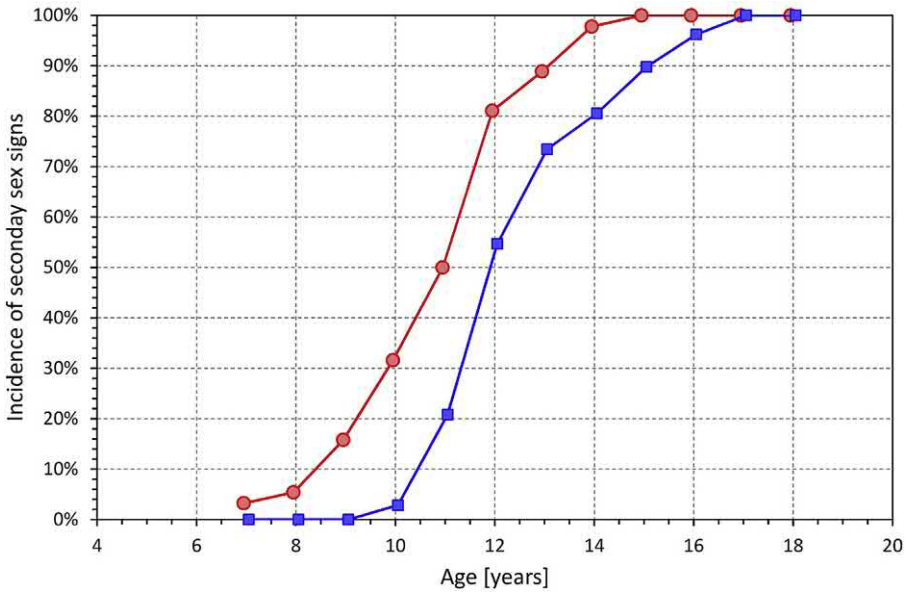

FIGURE 18.9 Incidence of secondary sex signs in age bands <8 years, 7−9 years, 8−10 years, etc. up to 16−18 years and >17 years (each shown approximately at the middle age of the band). Compare with the development of QTcI changes shown in the middle panel of Fig. 18.6. *Reproduced with permission from Andrsova I, Hnatkova K, Helanova K, Sisakova M, Novotny T, Kala P, et al. Individually rate corrected QTc intervals in children and adolescents. Front Physiol 2019;10:994. https://doi.org/10.3389/fphys.2019.00994.*

In this study, the log-linear regression formulae of QT/RR profiles such as Bazett or Fridericia corrections were not used intentionally because these might be potentially highly misleading. Moreover, it has been demonstrated in adult population that using fixed HR corrections is substantially incorrect if changes of HR more than 10 bpm are present [26].

No other studies of individual-specific QT/RR profiles in children and adolescents are available. Thus, only comparisons with adult data are possible: Similar HR spans were found in response to postural maneuvering in children as in described clinical investigations in young- to middle-aged adults before [23]. Also, the remarkable interindividual QT/RR profiles variability was confirmed in children as previously in adults [4,14]. The comparison between the linear and log-linear QT/RR regressions in children was similar as in adult data [27]. The averaged hysteresis constant close to 2 min is similar as previously reported in adult investigations [13,24].

Although the HR in girls was higher than boys, the differences were less pronounced than in adult population [28]. The reasons are unclear, which possibly may be similar as those for discrepancy between the secondary sex-sign maturity in females and their QTc prolongation. The regulatory equilibrium responsible for increased HRs in adult premenopausal females is probably dependent on prolonged autonomic conditioning in menstruating females [29].

To predict the duration of QT interval at a stable HR of 60 bpm, we used the projection of intrasubject curvilinear QT/RR regressions. The minimum HR was much higher in small children; thus, the projection had to be extrapolated (top panel of Fig. 18.2). In children, QT/RR correction to, for example, 80 bpm might prove more reliable.

In conclusion, we can say that opposite QTc changes occur in both sexes during adolescent years. These changes might be maintained by sex hormones in males, but in females, more complex mechanism must exist.

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Chapter 19

Electrophysiological changes during menstrual cycle

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The normal menstrual cycle in women lasts approximately 28 ± 7 days. Cycles less than 21 days and more than 35 days are considered pathological. Active menstruation bleeding occurs in the first 2−7 days of the menstrual cycle. It is usual for women to experience menstrual irregularities and anovulatory cycles below 20 and above 40 years of age, especially during the perimenopausal period.

At the beginning of a regular cycle, during the active bleeding period, serum estrogen and progesterone values are at the lowest possible level in all periods. In this period, the follicles in the ovaries begin to grow with the release of follicle-stimulating hormone (FSH) from the pituitary gland. As the dominant follicle develops, estradiol is released by the granulosa cells. This period is called "follicular phase."' Estradiol stimulates the release of luteinizing hormone (LH) with a positive feedback mechanism. Ovulation occurs approximately 16 h after the LH peak. After the ovulation, the corpus luteum is formed, and this structure is the primary source of sex steroids. With the ovulation, the corpus luteum begins to produce progesterone. This period is named as "luteal phase"—depending on the life of the corpus luteum. If pregnancy does not occur, the corpus luteum regrades. The life of the corpus luteum is 12−16 days, and the luteal phase lasts an average of 14 days. In the midluteal phase, which corresponds to the middle of this period, progesterone values are at the highest level in the blood.

The effects of sex hormones in menstrual cycle on cardiac electrophysiology

Hormonal changes throughout menstrual phases are not as prominent as in hormonal levels between the pre- and postmenopausal periods. However, it is crucial to understand the physiological mechanisms of menstrual phase variation in cardiac electrophysiology. Thus, researchers could explain the effects of sex hormones of intra- and intersexuality diversities. The electrophysiological effects of sex hormones are examined in another chapter of this book. Therefore, in this chapter, we will briefly discuss which hormones are effective during the menstrual cycle (Table 19.1).

Estrogens

The estrogen family consists of estrone (E1), estradiol (17-β E2), and estriol (E3). Among these, estradiol has the highest bioactivity. Serum estrogen levels begin to increase with the initial phase of the menstrual cycle, and this increase is continued until the ovulation between the 13th and the 16th day (follicular phase). Estrogen levels begin to decrease after ovulation and are at the lowest levels in this luteal phase (days 16−28). Postmenopausal estrogen concentrations are similar to males of the same age group [1] (Fig. 19.1).

The biological effects of estrogens occur via alpha and beta estrogen receptors (ERs). These receptors are involved in cardiac myocytes, fibroblasts, and endothelial cells [2,3]. ERs are involved in both the cytosol and the nuclear compartment. ER-α is present in the plasma membrane, T-tubules, and intercalated disks [4]. The effects of estrogens on nuclear receptors (so-called genomic effects) can occur during hours or days, while their impact on cytosolic receptors (nongenomic effects) can be seen in seconds.

Electrophysiological properties of estrogen

Estrogen has a negative inotropic effect [5]. This effect is caused by the inhibition of the voltage-dependent L-type

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TABLE 19.1 Electrophysiological effects of sex hormones.

Hormone	Parameter	Effect
Estrogens	Inotrophy Chronothrophy P-wave dispertion PR interval J-T $_{peak}$ interval T_{peak}-T_{end} interval SVT frequency	Negative Negative No effect No effect[a] Shortens[a] No effect[a] Negative correlation
Progesterone	P-wave dispertion Drug related QT prolongation SVT frequency and duration SVT induction	No effect Reverses Positive correlation Positive
Follicle Stimulating Hormone	Ventricular repolarization QTc	Prolongs Prolongs

SVT, supraventricular tachycardia; *QTc,* corrected QT interval.
[a]*with supraphysiological estrogen levels.*

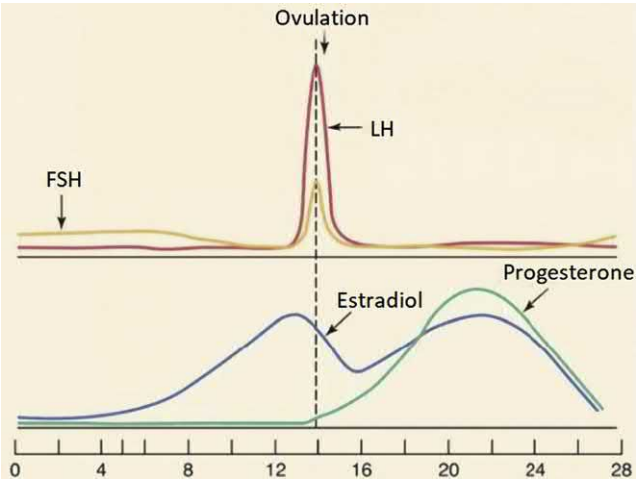

FIGURE 19.1 Hormonal fluctuations during the menstrual cycle. *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone.

calcium channel and the decrease of the inward calcium flow. It also shows the calcium antagonist effects by affecting Na^+/Ca^{2+} exchange [6]. Also, estrogens have negative chronotropic effects by suppressing T-type calcium channel flow, which is essential for pacemaker activity [7,8]. In addition to these effects on calcium metabolism, it has been speculated that estrogen downregulates potassium channels, thus prolonging the ventricular repolarization and naturally the QT interval [9]. However, these findings are debateful and are going to be discussed later in this chapter.

Progesterone

Progesterone is a 21-carbon steroid that is produced by the corpus luteum, placenta, and a small amount by follicles. It is in high concentrations in the luteal phase. Progesterone receptors in the cardiovascular system can be stimulated by estrogen. These receptors are expressed in vascular smooth muscle cells, endothelial cells, cardiac myocytes, and left atrial appendage myocytes [10–12]. Although there are limited data on the effects of progesterone on the cardiovascular system, it is presumed to have estrogen antagonist effects.

Electrophysiological properties of progesterone

During the luteal phase, progesterone levels are high and the QT interval is considered to be shorter by some authors [13,14]. Progesterone has a dominant role on ventricular repolarization in women and it was attributed mainly to slowly activating delayed rectifier potassium channels (IKs) enhancement and inhibition of L-type calcium channels through a nongenomic pathway [15,16]. This effect of progesterone on potassium and calcium channels explains the shorter duration of the action potential and QT shortening in the luteal phase. In addition, drug-induced QT interval (QT) prolongation has a negative correlation with progesterone [14].

Progesterone/estradiol ratio

Progesterone/estradiol ratio is negatively correlated with QTc in women [17]. Drug-induced QT prolongation has shown to be a negative correlation with that ratio [14].

Follicle-stimulating hormone

FSH prolongs ventricular repolarization and has a positive correlation to QTc in women [17]. The presence of FSH

receptors in the myocardium supports these findings [17]. Therefore, it is speculated that the FSH peak in the ovulatory phase increases the susceptibility to drug-induced QT prolongation [14]. In men with hypogonadism, the QTc interval is longer than in healthy men, but this does not apply to hypogonadotropic hypogonadism with low FSH [18–20]. Therefore, it is thought that QTc prolongation is not present while FSH values are low in these patients (Table 19.2).

Electrophysiological features of menstrual cycle

Atriums

P-wave abnormalities are associated with left atrial enlargement, left atrial hypertension, and altered conduction [21–23]. To determine these findings in ECG, P-wave morphology, duration, P-wave dispersion (PD), and PR dispersion are used. The difference between the maximal and minimal P-wave durations defines as PD. PD reflects intraatrial and interatrial conduction times and heterogeneous sinus impulse propagation. It is well known that inhomogeneous atrial conduction increases the risk of atrial fibrillation [24,25]. Increased PD is shown to be associated with atrial fibrillation in previous studies [24,25]. Karabag et al. [26] have found an association between PD and the menstrual cycle phases. In their study, the authors have reported that PD is significantly higher in the luteal phase than in the follicular phase.

In addition, they found a correlation between the day of menses and PD but no relationship between estrogen and progesterone levels with PD. Interestingly, the cause of PD increase in the luteal phase is not the longer maximal P-wave duration; it is a shorter minimum P-wave duration. Therefore, increased PD measurements are debateful and should be supported by other studies. In addition, increased sympathetic activity is shown to be related to PD [27]. Higher PD in the luteal phase may be attributed to autonomic tonus enhancement. Some researchers have reported that electrolyte fluctuations occur in different menstrual cycle phases, so altered electrolyte levels may effect the PD prolongation [28]. Similar to PD, PR interval dispersion has been studied in an observational study. PR dispersion is obtained by subtracting the minimum PR interval from the maximum PR interval [29]. They revealed the absence of a relationship between supraphysiological estradiol level and elevated risk of atrial arrhythmias, including atrial fibrillation.

Ventricular repolarization

QT-QTc interval

QT interval defines the time from the onset of the QRS complex to the end of the T-wave and expresses the duration of depolarization and repolarization of the ventricular myocardium. It varies according to age, sex, and heart rate. Corrected QT interval is the QT measurement performed by taking into account the QT shortening seen in increased heart rates and has commonly been calculated using Bazett's or Fridericia's formula.

QT interval is longer in premenopausal women than in men [30,31]. Women are also more susceptible to Torsades de Pointes (TdP) development when exposed to drugs that prolong the QT interval [32,33]. Also, the female sex is an independent risk factor for syncope and sudden death in patients with congenital long QT syndrome [34]. Susceptibility to TdP in females is attributed to sex hormones; it starts with puberty and then fades after menopause.

Some studies showed QT and QTc interval change with the menstrual cycle, and these fluctuations may lead to changes in the risk of arrhythmia in different menstrual phases [35]. Minor changes in ionic currents may increase

TABLE 19.2 ECG parameter changes with the menstrual cycle.

	Follicular Phase	Luteal Phase	Notes
P-wave dispersion		Higher[26]	
PR dispersion	No change	No change[29]	
QT interval	No change[a]	No change[a,14,37,38,39,40]	Reduced after DOB[37]
QTc interval	No change[a]	No change[a,39,41]	Reduced after DOB[41]
Ibutilid induced QT prolongation	Higher[14]		
QT/QTc dispersion	No change[a]	No change[a,19,29,39,45]	
J-T_{peak} interval		Shortened[29,39]	
T_{peak}-T_{end} interval	No change	No change[13,39]	

DOB, double autonomic blockade, *QTc*, corrected QT interval.
[a]*Conflicting results. General opinion was written to the table.*

the susceptibility to arrhythmias by altering the action potential morphology and causing repolarization abnormalities or QT/QTc prolongation [36]. Cardiac action potential (AP) morphology has an essential role in arrhythmia formation. The depolarizing inward and repolarizing outward flows, intracellular ion concentrations, transmembrane potentials, and ion channel expressions determine the morphology of the action potential and the electrophysiological properties of cardiomyocytes. The results of studies declaring the effect of hormonal changes during menstrual cycle on QT and QTc interval are contradictory. Nakagawa et al. revealed that both QT and Q-T_{peak} (the interval between the onset of Q wave and the apex of T-wave) intervals were 2.4% (approximately 10 ms) shorter during the luteal phase of the menstrual cycle when compared with the follicular phase. They have attributed that to the progesterone effect which reverses the estrogen-induced QT prolongation [13]. However, QT shortening in the luteal phase may not be protective against ventricular arrhythmias due to increased sympathetic activity; thus critical disturbances may nevertheless occur. On the contrary, the majority of other studies showed no significant changes in QT/QTc interval durations through the menstrual cycle [14,37–41]. Burke et al. have reported that QT interval did not significantly change between basal menstrual cycle phases; however, QT was reduced in the luteal phase after double autonomic blockade with atropine and propranolol [37]. Endres et al. [41] have found similar results: QTc has differed after the double autonomic blockade and was the shortest in the luteal phase and followed by menstrual and follicular phases. Dogan et al. [39] have conducted a study with 38 volunteers and found a numeric QTc shortening which was not statistically significant. One reason for this discrepancy in current studies may be because of the fact that patient data collection is not sensitive enough and biological variables are not sufficiently accountable. In general, it can be speculated that QT and QTc do not change in menstrual cycle phases, but autonomic tonus is closely related to the action potential and should be taken into account.

A study investigating the effects of a QT prolonger drug "ibutilide" during the menstrual cycle and QT interval showed that while ibutilide-associated QTc prolongation is the highest in menstruation, it is followed by the ovulation and the luteal phase [14]. Furthermore, they found that progesterone levels were inversely correlated with ibutilide-induced QTc prolongation. This is attributed to the protective effect of progesterone in luteal phase [42].

QT-QTc dispersion

QT dispersion (QTd) is measured as the difference between the longest and the shortest QT distances on the 12-lead surface ECG. Corrected QT dispersion (QTcd) is calculated as the difference between the maximum and the minimum corrected QT distances. Increased QTd indicates heterogeneity in ventricular repolarization, which is associated with an increased risk of ventricular arrhythmia and sudden cardiac death [43,44]. There are few studies showing the relationship between QT dispersion and menstrual cycle and there is no consensus on this issue. More studies show that there is no relationship between the menstrual cycle and QT dispersion [14,29,39,45]. However, Uckuyu et al. have reported a study which indicates that QT dispersion is shortened by ovulation [46].

J-T_{peak} interval

The J-T_{peak} interval defines the distance from the J point to the peak of the T-wave. It is a reliable indicator of repolarization and it refers to early repolarization. J-T_{peak} interval prolongation is considered as a risk factor of mortality similar to QT prolongation [47–49]. Although the number of studies on this subject is very limited, Dogan et al. have released a study indicating that J-T_{peak} and corrected J-T_{peak} interval are shortened with the ovulation [39]. There is also a study demonstrating J-T_{peak} shortening with supraphysiological estrogen levels in in vitro fertilization therapy [29]. The authors attribute the J-T_{peak} shortening with estradiol to its Ca^{++} channel inhibitory effects. However, more comprehensive studies are necessary on this topic.

T_{peak}-T_{end} interval

T_{peak}-T_{end} (T_{p-e}) is the distance between T-wave peak point and the returning point to the isoelectric line. The T_{p-e} interval reflects the transmural dispersion of repolarization [50]. Some studies revealed a relationship between T_{p-e} and ventricular arrhythmias, heart failure, and sudden cardiac death [51,52]. T_{p-e} prolongation suspects a potential tendency to reentrant arrhythmias [29]. There is no difference in T_{p-e} measurements in both physiological and supraphysiological estrogen levels [13,29,39]. However, Nakagawa et al. suggested that T_{p-e} does not change with the ovulation but the interval from QRS onset to T_{peak} is shorter in the ovulation than in the menstruation [13].

Arrhythmias

Clinicians should identify the relationship between arrhythmias and menstrual cycle and remember that the menstrual cycle may affect arrhythmia induction during electrophysiology testing. The frequency of supraventricular tachycardia (SVT) is higher in the luteal phase of the menstrual cycle and is inversely correlated with the serum estrogen levels [42]. Some authors have found a significant positive correlation between plasma progesterone levels

and the number of episodes and duration of SVT and a significant inverse correlation between plasma estradiol and SVTs [53]. Rosano et al. have reported that the acute administration of 17-β estradiol into right atrium prolongs the right intraatrial conduction time, intranodal conduction time, and right atrial effective refractory period. As a result, SVT risk is reduced with estradiol [54]. Estrogen also has calcium blocking effects similar to verapamil. As a result, electrophysiological studies for SVT induction are more successful when performed during the luteal phase. This should be taken into account for arrhythmia detection and ablation procedures [55]. Unfortunately, there is no randomized controlled study on this topic. On the other hand, Sugishita et al. have reported an atrial fibrillation case about more frequent symptoms in the follicular phase, which parasympathetic nervous system is dominantly activated [56]. Authors changed antiarrhythmic drugs from daily to periodic administration a couple of days before the menstrual cycle and symptoms decreased with this approach. These findings speculate that the SVT tendency is attenuated by estrogen and facilitated by progesterone.

Increased sympathetic activity in the luteal phase may lead to ventricular arrhythmias, especially at the end of the cycle, namely perimenstrual period. Previous studies investigating the relationship between the menstrual cycle and the frequency of ventricular arrhythmias have shown that these arrhythmias are more common in the perimenstrual period, especially before the onset of menses [57–59].

Ventricular premature beat and ventricular tachycardia

In women, right ventricular outflow tract (RVOT) ventricular arrhythmias are twice as frequent as men [60]. Also, women are more prone to the congenital long QT syndrome, risk of drug-induced TdP development, and idiopathic RVOT ventricular tachycardia (VT) formation [61]. The differences in risk of ventricular arrhythmias between male and female sex suggest the effects of sex hormones on the cardiac action potential. Our knowledge is less regarding the effects of menstrual cycle on the supraventricular and ventricular premature beat. Fuenmayor et al. [62] have conducted a study with 25 volunteers and found no relationship between menstrual cycle phases and both supraventricular and ventricular premature beats. Despite the vast majority of patients complained of arrhythmia aggravation during the perimenstrual period, Holter monitoring was not able to detect any worsening of arrhythmia or heart rate changes. Dogan et al. [39] have reported the opposite opinion. They have examined 38 premenstrual women and found that RVOT ventricular premature beats had decreased with the ovulation.

There are limited data on the relationship between ventricular tachycardia and the menstrual cycle. Marchlinski et al. [57] have reported that RVOT VT can be triggered by the menstrual hormonal flux in women. They have observed a significant increase of RVOT VT in perimenstrual period (within 2 days of the onset and during the first 1–2 days of menses). However, that cannot be explained with the lack of estrogens while pregnancy or postmenopausal state studies do not support these findings. Instead, increased levels of circulating catecholamines or enhanced effects of catecholamines in the luteal phase may be responsible for this triggering. Serum norepinephrine levels increase with the premenstrual period [63–65]. Increased norepinephrine seems to be more likely to trigger RVOT VT than estrogen.

These small-scale studies that attempt to determine the relationship between menstrual cycle with atrial and ventricular tachycardias show us the following: we do not have sufficient data to show the causal relationship between menstrual cycle hormones and atrial or ventricular rhythm disorders. However, while arrhythmia induction and ablation are aimed at the electrophysiology laboratories, timing arrangement according to the menstrual cycle of the patients may be considered. Furthermore, noninvasive therapeutic strategies of the patients can be arranged according to the periods mentioned above. In selected patients, it may be suitable to design the antiarrhythmic or symptom-relieving medications in regard to the perimenstrual period. Thus, patients are protected from potential side effects and daily medication may not be needed.

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Chapter 20

Electrocardiographic changes after heart transplantation

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Introduction

Orthotopic heart transplantation is a well-established therapy for end-stage heart failure patients. The median survival of adult patients transplanted after the year 2000 exceeds 12 years, for those who survive the first posttransplantation year is expected to reach 15 years [1]. This text will describe morphological changes of electrocardiogram (ECG) following heart transplantation with special attention to QT interval where the sex-related differences are most pronounced. Then particular types of arrhythmias will be commented. In the end, the phenomenon of sudden cardiac death in the specific population of posttransplantation patients is discussed.

Electrocardiogram after heart transplantation

Morphological changes

Interestingly, most of the studies describing ECG in heart transplant recipients were made in the last century [2–4]. Recent study evaluated serial ECGs in 98 patients in the first year following heart transplantation, and the most common abnormalities were intraventricular conduction delay or block, mostly right bundle branch block (RBBB). Sex differences were not addressed in the analysis [5]. RBBB has been also suggested as a marker of rejection, but the evidence is inconsistent and, again, sex differences have not been studied [6,7].

QT interval

In heart transplant patients, QT and QTc intervals have been suggested as predictors of rejection and sudden death. This hypothesis was tested in several small studies analyzing little above 200 individuals. QTc interval prolongation over 20 ms was observed in patients with mild or severe rejection [6], and in the other study, prolongation of QTc was associated with sudden deaths [8]. Small numbers did not allow for any sex-specific analyses. Interestingly, none of the studies addressed the importance of sex-specific differences in QT interval duration resulting in pronounced differences in normal values.

Electrocardiographic patterns and characteristics undergo marked changes during the life of an individual. A lot of these changes are sex-specific [9]. The most pronounced one is the difference in duration of ventricular repolarization for which the QT interval is used as a surrogate on the surface ECG [10].

While QT interval duration is quite similar in boys and girls, in adulthood it is significantly longer in females [11]. It is ridiculous that more than a century after introduction of ECG it has not been known what happens to QT interval in particular sexes in adolescence. Only very recently, preliminary data have become available that during adolescence the QT interval shortens in males and prolongs in females simultaneously (see Chapter 19 of this book). Nevertheless, mechanisms underlying these changes remain unclear. The reason can be either sex difference in hormones or sex difference in tissue and ion channels. Experimental

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studies performed in a variety of animal models have shown that sex hormones exert genomic effects on protein synthesis of some ion channels, their posttranslational modifications, and on ion channel function mediated by signal transduction pathways. Human data are limited [12–14].

From that point of view, heart transplant recipients can serve as an interesting model when sexes of the recipient and the donor are different. This situation enables an observation of a behavior of a heart of one sex in the hormonal environment of the opposite sex.

This concept was used in a small study performed by our group [15]. The study faced several unexpected problems. First, in a group of more than 200 heart transplant recipients, about three-fourth were males with hearts from male donor compared with less than 10% males with female hearts. Such disproportions are based on following facts: the donors are mostly males because of their more risky lifestyle, heart failure in women occurs later, and smaller female hearts cannot by transplanted into larger male chests and vice versa [16]. Thus, ECG recordings were possible in 20 males with male hearts, but on the contrary to original plan in only 14 females with male hearts, 13 females with female heart, and 11 males with female hearts. There is currently little chance to increase these numbers because of increasing evidence that donor–recipient sex mismatch is predictor of early and late rejections and long-term adverse events following heart transplantation. Recent study has shown that in adults especially in male recipients receiving female hearts, the risk for early and late major rejections is significantly increased [17]. The sex mismatch importance was confirmed in a large study with pediatric heart transplantation recipients; nevertheless, the results were bit different—long-term survival was lowest in female recipients of male hearts. Interestingly, in this study, males receiving female hearts had a slightly lower allograft survival at 5 years, but that difference disappeared in long-term survival when adjusting for other risk factors [18]. Similar relationships have been observed also for other organs transplantation; for liver, female-to-male mismatch represents the worst combination [19]. Among recipients of the kidneys, sex mismatch impact was also present, however, in age-dependent manner [20].

In our study, ECGs were also obtained from 20 healthy males and 20 healthy females for control purposes. During continuous ECG recording, all investigated individuals underwent autonomic provocative test consisting of five different postural stages each of 8 min durations (supine, unsupported sitting, supine, unsupported standing, and supine).

Reliable QT interval measurements are based on a possibility of a precise determination of the end of a T wave. And that was another problem. In heart transplant recipients, T waves were often flat, biphasic, or of even more complex morphology (Fig. 20.1).

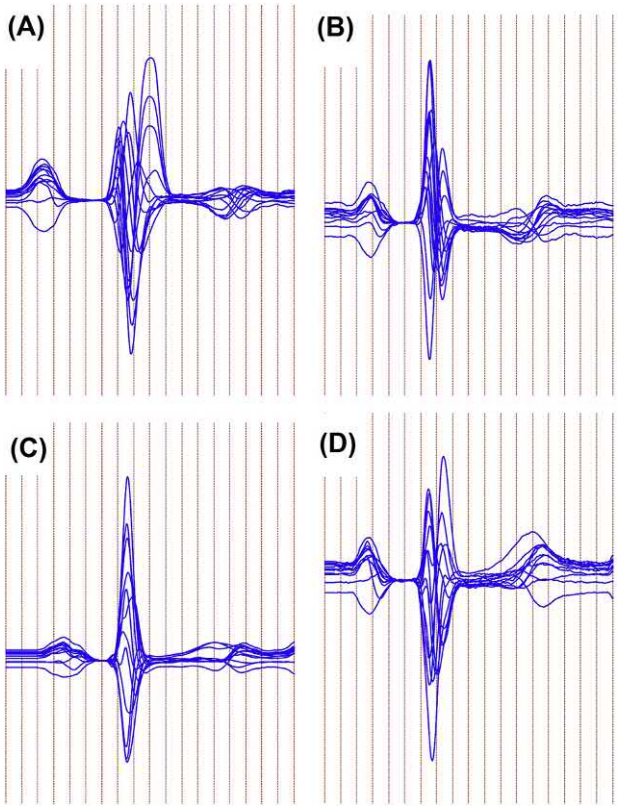

FIGURE 20.1 Examples of electrocardiogram representative median beats with all 12 leads superimposed on the same isoelectric line in four heart transplantation patients. Vertical gridlines are shown in 40 ms steps. (A) 69-year-old male 13.5 years after heart transplantation of a male heart; (B) 72-year-old female 13.7 years after heart transplantation of a male heart, (C) 66-year-old female 2.1 years after heart transplantation of a female heart; (D) 23-year-old male 2.2 years after heart transplantation of a female heart. *Reprinted from Novotny T, Leinveber P, Hnatkova K, Reichlova T, Matejkova M, Sisakova M, et al. Pilot study of sex differences in QTc intervals of heart transplant recipients. J Electrocardiol 2014;47:863–68. With permission from Elsevier.*

Moreover, autonomic provocative maneuvers lead to very variable heart rate responses, and in majority of investigated individuals, the heart rate changes were only narrow (Fig. 20.2) and the QT/RR relationships were clearly different from healthy subjects (Fig. 20.3) [21]. This phenomenon is linked to the fact that a transplanted heart is completely denervated. Although it is now clear that reinnervation is possible and has been observed as early as 1 year after the transplantation, the duration and extent of the process are uncertain [22,23]. In our study, we observed not only substantial heart rate changes during postural maneuvers not later than 1 year after the transplantation but also very limited heart rate response more than 10 years after transplantation suggesting that the process of reinnervation is very individual.

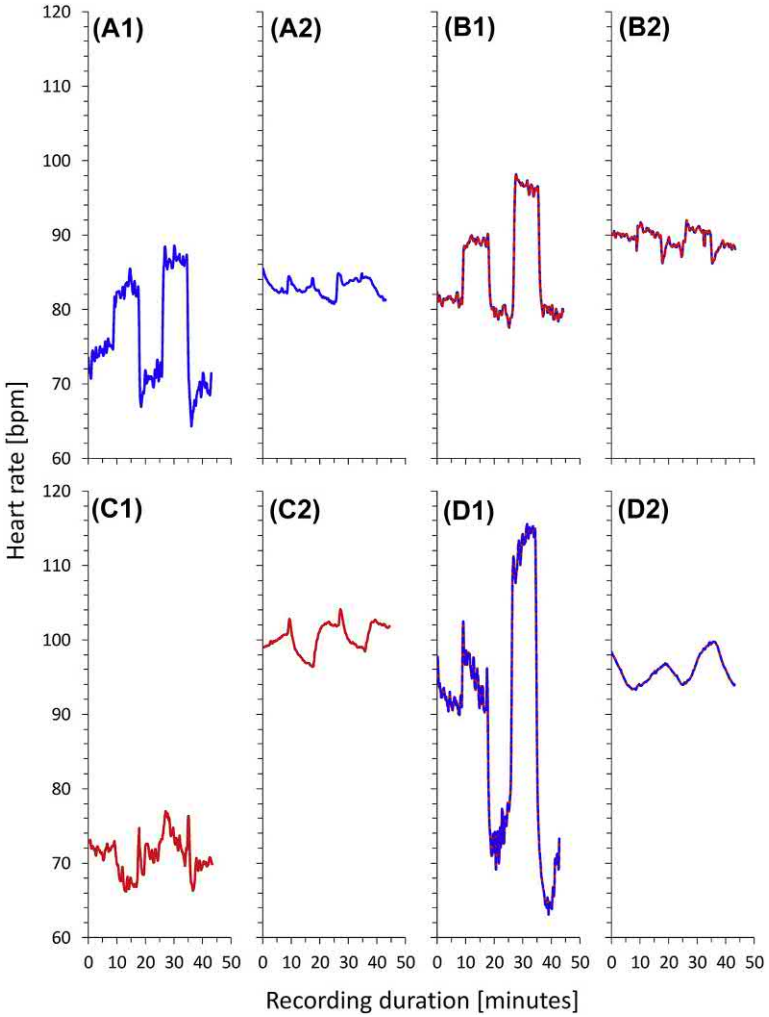

FIGURE 20.2 Examples of heart rate responses to postural provocative maneuvers in eight heart transplantation patients. Cases A2, B2, C2, and D2 correspond to cases A, B, C, and D shown in Fig. 20.1, respectively. (A1) 56-year-old male 7.3 years after heart transplantation of a male heart; (B1) 72-year-old female 13.7 years after heart transplantation of a male heart; (C1) 66-year-old female 3.9 years after heart transplantation of a female heart; (D1) 22-year-old male 1.4 years after heart transplantation of a female heart. *Reprinted from Novotny T, Leinveber P, Hnatkova K, Reichlova T, Matejkova M, Sisakova M, et al. Pilot study of sex differences in QTc intervals of heart transplant recipients. J Electrocardiol 2014;47:863–68, with permission from Elsevier.*

Because of the narrow ranges of RR intervals, neither individual QT/RR hysteresis nor individual QTc corrections [24] could be used. Thus, being aware of all the limitations, a preliminary analysis was performed using the general hysteresis model (the exponential decay model leading to 2-min 95% adaptation of QT interval to RR interval changes) [25,26] and Fridericia correction formula [15,27].

As expected, the average QTc values were significantly higher in the group of healthy females compared with healthy males proving the capability to detect the sex differences in the QTc intervals even with these small numbers of individuals. On the contrary there was no statistically significant difference between any particular groups of heart recipients. Nevertheless, when pooled together, female patients (irrespective of the sex of the heart donor) had longer QTc interval (445.6 ± 20.0 ms) compared with male patients (436.1 ± 21.6 ms), and the difference did almost reach statistical significance ($P = .09$) (Fig. 20.4).

Analysis of data from this project has not been fully finished yet, and the above-described results have very preliminary character (being based on only automatic measurements of QT intervals and using universal heart rate and hysteresis correction).

Despite the above-mentioned limitations, the data suggest that the sex of donor plays limited, if any, role in the sex-related QT interval duration differences, which are more likely related to different hormonal environment of heart recipient.

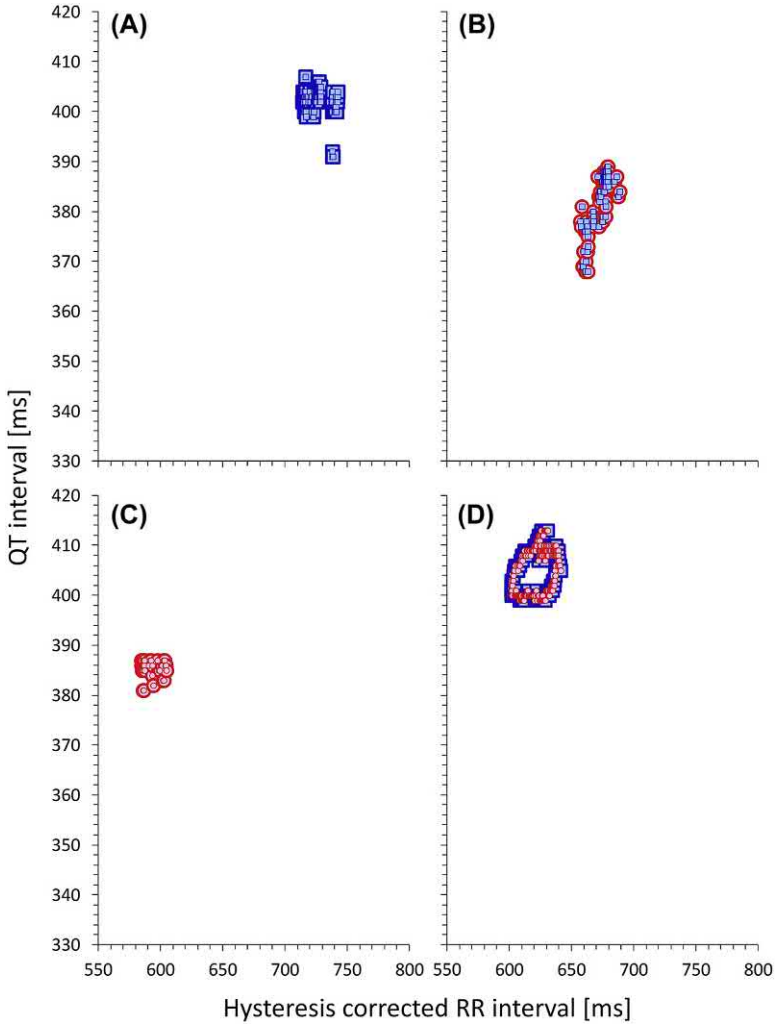

FIGURE 20.3 Examples of scatter diagrams of the QT/RR relationship in four heart transplantation patients. The cases are the same as shown in Fig. 20.1. Note that the RR intervals were obtained after generic correction for QT/RR hysteresis that was clearly inappropriate in patient D. *Reprinted from Novotny T, Leinveber P, Hnatkova K, Reichlova T, Matejkova M, Sisakova M, et al. Pilot study of sex differences in QTc intervals of heart transplant recipients. J Electrocardiol 2014;47:863–68, with permission from Elsevier.*

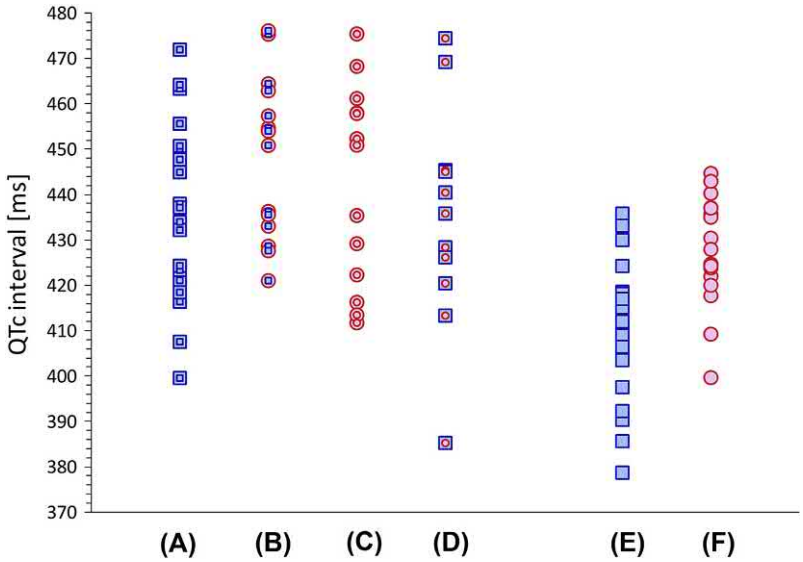

FIGURE 20.4 Averaged QTc intervals in individual study subjects. *Red circles* and *blue squares* correspond to female and male subjects, respectively. Heart transplantation patients are shown with *small red circles* and *blue squares* in the center of the marks that correspond to patients who received hearts from female and male donors, respectively. Healthy controls are shown without any central marks. Lettering of the horizontal axis indicated study groups. *Reprinted from Novotny T, Leinveber P, Hnatkova K, Reichlova T, Matejkova M, Sisakova M, et al. Pilot study of sex differences in QTc intervals of heart transplant recipients. J Electrocardiol 2014;47:863–68, with permission from Elsevier.*

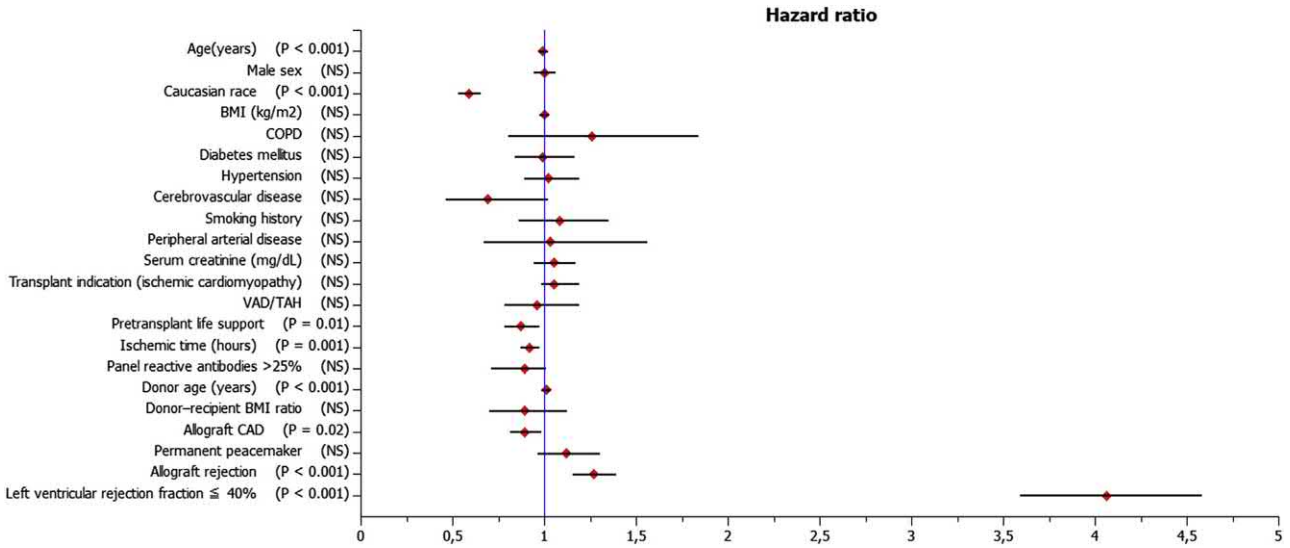

FIGURE 20.5 Univariate predictors of sudden cardiac death (n = 1659) versus survivors following heart transplantation (n = 20,168). In this specific population, number of sudden cardiac deaths (SCDs) did not differ between sexes, on the contrary to general population, where risk for SCD in men is at least twice that of women in all age groups. *Modified from Vakil K, Taimeh Z, Sharma A, SyedAbidi K, Colvin M, Luepker R, et al. Incidence, predictors, and temporal trends of sudden cardiac death after heart transplantation. Heart Rhythm 2014;11:1684–90.*

Atrial arrhythmias in heart transplant recipients

Sinus node (SN) dysfunction occurs in 5%–20% of patients with transplanted heart [28,29]. In a recent study in a group of 1179 heart transplant recipients, 118 patients required pacemaker implantation because of post-transplantation SN dysfunction. However, almost 96% of these patients had received the transplant by biatrial surgical approach, which was the most important risk factor for SN dysfunction. Currently the biatrial approach has been abandoned and replaced by bicaval surgical technique. No sex differences were observed in this study [30].

Atrial flutter (cavotricuspid isthmus dependent) was the most common arrhythmia in patients after heart transplantation observed in majority of studies (in up to 10%). Atrial fibrillation seems to be rare in stable patients. Incidence of scar-related atrial arrhythmias has decreased dramatically after introduction of bicaval surgical method. In any of above-mentioned arrhythmias, no sex-related differences have been observed [31–33].

Sudden death after heart transplantation

Sudden cardiac death (SCD) has been recognized as a significant cause of death in heart transplant recipients for decades. Several years ago, this topic was addressed in a large set of US patients. In a cohort of over 37,000 individuals, approximately 10% died suddenly. While the cumulative incidence of SCD was higher than in general population, its proportion to other ways of death was similar [34]. Interestingly, in this specific population number of SCDs did not differ between sexes (Fig. 20.5), on the contrary to general population, where SCD is more common in males compared with females in all age groups [35]. Putative mechanisms underlying higher proportion of SCDs in posttransplant females are completely unknown.

Acknowledgments

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Chapter 21

Cardiac rhythm changes during menopause

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Introduction

Menopause, by definition, is the permanent cessation of menstrual cycles in women after a certain age. The average age onset of menopause is 51 years [1]; however, it may be affected by many factors notably genetic and smoking [2,3]. Menopause is clinically diagnosed by amenorrhea for 12 months and characterized by decline in estrogen production in the women's body [4].

Age of menopause has been associated with cardiovascular disease risk. Risk of ischemic heart disease and stroke is increased in women with a natural earlier age of menopause. Additionally, surgical menopause is associated with almost double the risk of ischemic heart disease. On the other hand, exogenous estrogen use in postmenopausal women has been associated with decreased risk of ischemic heart disease.

Despite the numerous data on the association between menopause and cardiovascular disease risk, particularly, ischemic heart disease, there is very limited literature on the relationship between arrhythmias and menopause. There is overlap between risk factors relating to aging and the menopause which makes it difficult to tease apart each individual contribution. This book chapter will examine the current knowledge on the association of menopause and cardiac arrhythmias in the larger context of sex differences.

Electrophysiological sex differences in supraventricular tachycardias

Atrioventricular reentrant tachycardia and atrial fibrillation (AF) are more common in men compared to women. However, women have a higher incidence of atrial tachycardia and atrioventricular nodal reentrant tachycardia (AVNRT) (Fig. 21.1) [5].

Supraventricular tachycardias (SVTs) are known to be less common than other types of arrhythmias. In fact, their prevalence is around 0.42%, whereas their incidence is as low as 0.51 per 1000 person years [6]. In the United States, approximately 90,000 SVT cases are detected each year [7], and 25% of SVT cases that present for medical attention in emergency departments ends up being hospitalized [8].

Taneja et al. [9] have demonstrated that women have shorter sinus cycles compared to men. They also have shorter sinoatrial node recovery time, HV interval, and QRS duration [9]. Prior studies have shown that women exhibit higher resting heart rates compared to men [9,10]. Burke et al. reported shorter sinus cycle length in women during the luteal phase of the menstrual cycle [10]. Similarly, Rosano et al. [11] have conducted a study on a small group of premenopausal women to assess the occurrence of SVT in relation to the menstrual cycle

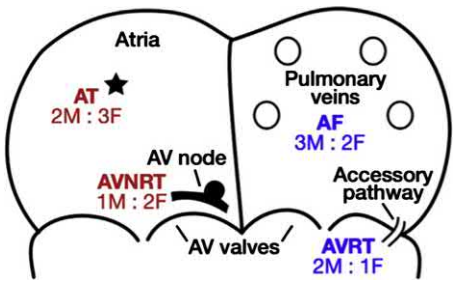

FIGURE 21.1 Sex differences in supraventricular arrhythmias susceptibility. *AF*, atrial fibrillation; *AT*, atrial tachycardia; *AV*, atrioventricular; *AVNRT*, atrioventricular node reentrant tachycardia; *AVRT*, atrioventricular reentrant tachycardia. *Reproduced with permission Tadros R. et al. Sex differences in cardiac electrophysiology and clinical arrhythmias: epidemiology, therapeutics, and mechanisms. Can J Cardiol 2014;30(7):783–92.*

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phases. Results showed that SVT and symptomatic episodes take place more frequently during the luteal phase of the menstrual cycle [11]. Hence, SVT are more prone to occur with low estrogen and high progesterone levels, indicating an inversely proportional correlation between SVT and estrogen level (Fig. 21.2) [11].

Suenari et al. [12] have shown that compared to premenopausal women with AVNRT, postmenopausal women patients had longer AH interval, atrial effective refractory period (ERP), ventricular ERP, anterograde slow pathway (SP) ERP, and retrograde SP ERP. In addition, a significantly higher proportion of postmenopausal women required isoproterenol and/or atropine for tachycardia induction, in addition to pacing maneuvers, compared to premenopausal women [12].

Similarly, Liuba et al. [13] have shown that women had shorter sinus cycle length, HV interval, AV nodal ERP, AV block cycle length, and tachycardia cycle length. The increased incidence of AVNRT in women compared to men is attributed to a wider "tachycardia window," which is the difference between the fast and SPs refractory periods, as women have shorter AV nodal ERP but equal fast pathway ERP [13]. The shorter AV nodal ERP in women compared to men was also demonstrated in postmenopausal women suggesting that nonhormonal factors could be contributing to the electrophysiologic sex-related differences [13].

Acute administration of estradiol 17 beta has been shown to prolong intraatrial conduction time, intranodal conduction time, and right atrial ERP in a randomized study including 18 postmenopausal women who were referred for a follow-up evaluation after radiofrequency ablation for supraventricular tachyarrhythmias [14]. This suggests that lack of estrogen during menopause may be associated with an increased incidence of palpitations and worsening preexisting arrhythmias.

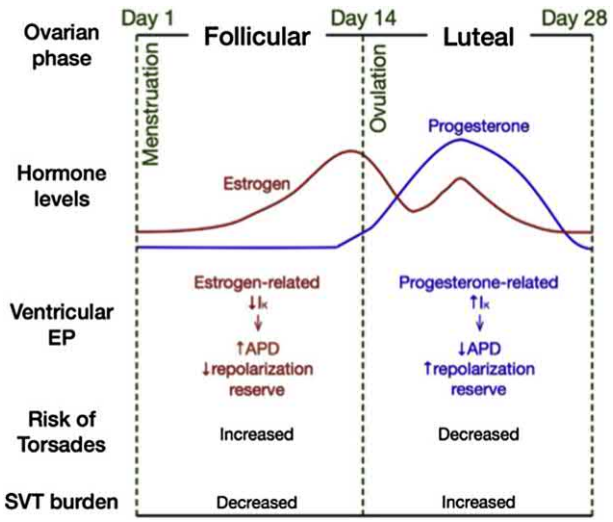

FIGURE 21.2 Electrophysiological changes and arrhythmia susceptibility during female ovarian cycle. Red—follicular phase properties; blue—luteal phase properties. *APD*, action potential duration; *EP*, electrophysiology; I_K, delayed rectifier K^+ current; *SVT*, supraventricular tachycardia. *Reproduced with permission Rosano GM. et al. Cyclical variation in paroxysmal supraventricular tachycardia in women. Lancet 1996;347(9004):786–88.*

Atrial Fibrillation

AF is the most common arrhythmia and it is a rapidly growing health care concern. The risk of AF increases with increasing age; AF is estimated to affect around 1% of the general population. However, the risk increases to at least 8% in elderly population above the age of 80 years [15]. 70% of all AF patients are between the ages 65 and 85 years [15]. Although the risk of AF is higher in men, the absolute number of AF cases is at least similar in patient > 75 years of age as there are more women than men aged > 75 years [16]. Based on the Framingham study, the lifetime risk of AF in women at the age of 40 is almost 1 in 4 [17]. Multiple risk factors have been shown to contribute to the development of Atrial Fibrillation in female patients (Fig. 21.3). Table 21.1 summarizes important sex differences in AF in terms of risk, comorbidities, management, and outcomes.

AF incidence and age of menopause

The Framingham Heart Study [18]:1809 female participants, with mean age of 71.4 years and mean age of menopause of 49.8 years, were analyzed for AF events. Participants with menopausal age of <45 had an AF incidence rate of 15.8 per 1000 person years, whereas those with menopausal age of 45–53 had an AF incidence rate of 11.5 per 1000 person years and participants with menopausal age of >53 had an AF incidence rate of 13.3 per 1000 person years. No statistically significant association was found between age of menopause and AF incidence (Fig. 21.4).

The Women's Health Study (WHS) [19]: Analysis of 30,034 participants in the WHS prospective study, with a median age of 53 years and median age of menopause of 50 years, concluded no significant association between AF incidence and age of menopause. A weak, statistically insignificant, trend of lower AF risk was found among women with a menopausal age of < 45 years.

AF incidence and postmenopausal hormone therapy

The association between postmenopausal hormone therapy (PHT) and AF incidence has been controversial. To date, three studies have looked at the relationship between PHT and AF incidence [19–21]. In a retrospective cohort study including 5489 postmenopausal women treated with either estradiol (1815 women) or conjugated equine estrogens

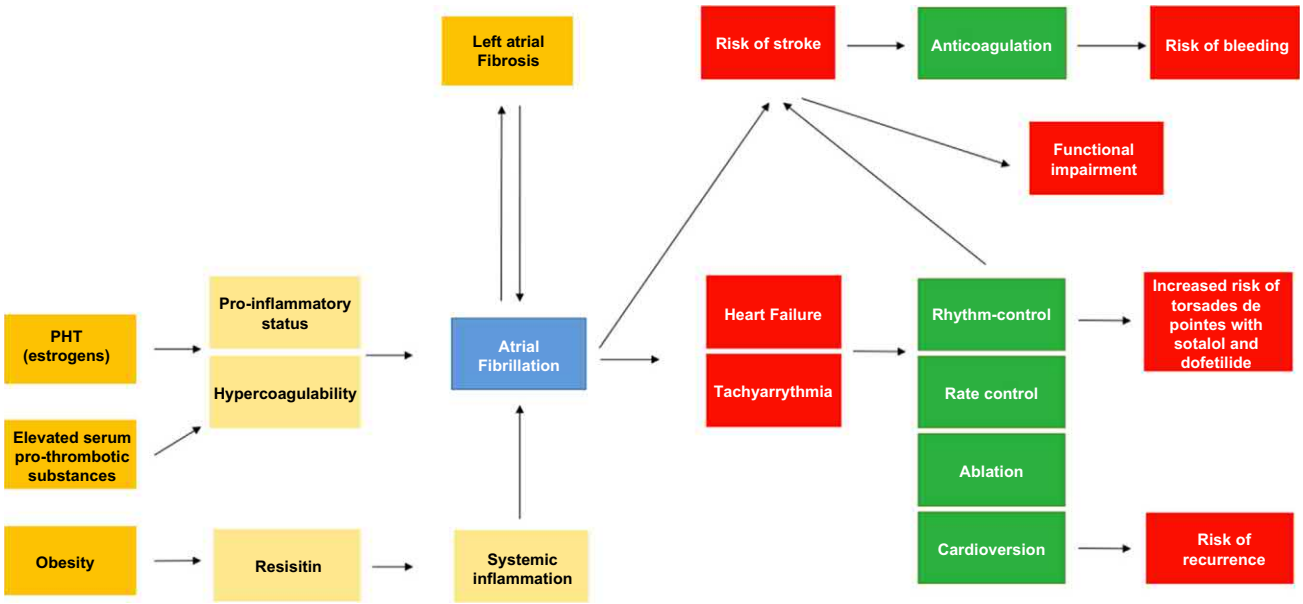

FIGURE 21.3 Postulated association between risk factors and outcomes in relation to atrial fibrillation in female sex.

(CEEs) (3674 women), those treated with CEE had a significantly increased AF incidence with an adjusted hazard ration of 1.96 [20].

The Women's Health Initiative study [21] randomized postmenopausal women to three groups: placebo, CEE in addition to medroxyprogesterone acetate in women with a uterus, and CEE alone in women posthysterectomy. Hysterectomized women who received CEE alone had a significantly higher incidence of AF. However, women who received CEE plus progestins did not have an increased incidence of AF compared to placebo group (Fig. 21.5).

Similar findings were demonstrated in the WHS [19], which concluded that use of estrogen-alone PHT was associated with increased AF risk, whereas the use of estrogen plus progesterone was not.

One theory is that CEE and its metabolites may be proinflammatory, which may increase blood hypercoagulability and trigger AF.

Left atrial structure, AF, and female sex

Postmortem histopathological analysis has shown a relationship between left atrial fibrosis and AF [22,23]. The DECAAF study demonstrated that the degree of atrial fibrosis was an independent risk factor for AF recurrence postablation [24]. Late-gadolinium enhancement MRI (LGE-MRI) fibrosis quantification of left atrium showed that aging female patients had more extensive left atrial fibrosis compared to male patients (Fig. 21.6) [25]. Increased left atrial volume has been considered as an important risk factor for AF development [26]. Women with "surgical" early menopause exhibit a statistically significant prolongation in interatrial electromechanical delay compared to women with similar demographic data and left atria size [27]. Increased intraleft atrial mechanical delay, the time period between the beginning of the P wave to the beginning of the A wave, has been demonstrated to be prolonged in patient with paroxysmal AF [28]. It has been identified as an early echocardiographic sign for paroxysmal AF detection [29]. Interatrial electromechanical delay is thought to alter the spread of sinus pulses, which increases susceptibility to AF [27].

AF, stroke, and female sex

The ATRIA study, a prospective study with 13,559 adult AF patients, has shown that female patients had increased risk of AF-related thromboembolic complications compared to male patients while off warfarin therapy [30]. Female sex was found to be an independent risk factor for thromboembolism in AF patients [31]. The increased risk of stroke in AF patients has been also demonstrated in other studies [32–34]. It is still unclear why female sex is an independent risk factor for thromboembolism. Studies have shown higher levels of prothrombotic substances in women compared to men, such as prothrombin fragment F1.2, von Willebrand factor, and tissue plasminogen activator antigen. Additionally, as mentioned earlier, female patients had more extensive left atrial fibrosis based on LGE-MRI compared to male patient, which is by itself associated with increased risk of stroke in AF patients [25,35]. Female sex was accounted for in the CHA2DS2VASc risk score,

TABLE 21.1 Sex differences in atrial fibrillation (AF) risk, comorbidities, management, and outcomes.

Factor	Sex differences
AF incidence risk	• The absolute number of AF cases is at least similar in patient > 75 years of age [16]. • After age 75 years, about 60% of the people with AF are women [16]. • No statistically significant association exists between age of menopause and AF incidence [18,19]. • CEE PHT associated with significantly increased AF incidence [19–21].
Comorbidities	• Overall risk of HF was almost similar in both sexes [62]. • HF with preserved systolic function was more frequent among women [63]. • Female patients are older [64]. • Female patients have increased prevalence of hypertension [65,66], valvular heart disease [67],diabetes [67], and thyroid disease [59].
Anticoagulation	• Prevalence of anticoagulation use is similar in male and female patients [61]. • Possible increased risk of bleeding in female patients on warfarin [59]. • Female patients have greater reduction in thromboembolism risk with warfarin compared to male patients [30].
Rhythm control versus rate control	• No significant difference in survival exists between rate control and rhythm control [50]. • Female patients have greater incidence of Torsades de pointes with the use of class IA and III antiarrhythmics (risk of Torsades de pointes was doubled with the use of dofetilide or sotalol but to a lesser extent with the use of amiodarone) [15,53]. • Female patients treated with rhythm control have more hospitalizations for heart failure and thromboembolic complications compared to rate-control treated patients. • Female patients with persistent AF had increased incidence of death in rhythm-control approach compared to rate-control approach [54].
Ablation	• Female patients are less likely to receive AF catheter ablation [68,69]. • AF ablation success rate is similar between female and male patients [55,56,65]. • Female patients have higher risks of early complications of hemorrhage and tamponade [57]. • Female patients are less likely to undergo repeat ablation procedures [57]. • More female patients undergo AV-node ablation compared to male patients [58].
Cardioversion	• Female patients experience higher recurrence rate of AF after electrical cardioversion [70]. • Female patients carry an increased risk of thromboembolic events after electrical cardioversion [71].
AF complications	Stroke: • Female sex is an independent risk factor for thromboembolism in AF patients [31,32]. • Female patients have more extensive left atrial fibrosis based on LGE-MRI compared to male patients, which is associated with increased risk of stroke in AF patients [25]. Quality of life (QoL): • Female patients report lower experienced quality of life compared to male patients [33].

which showed an improved predictive value for thromboembolism over the CHADS2 score [36]. In fact, female sex had the highest odds ratio as a risk factor for thromboembolic events among the rest of CHA2DS2VASc risk score components [36].

Obesity, physical activity, and AF risk in postmenopausal women

Obesity has been identified as a modifiable risk factor for AF development [37–39]. Wanahita et al. reviewed 16

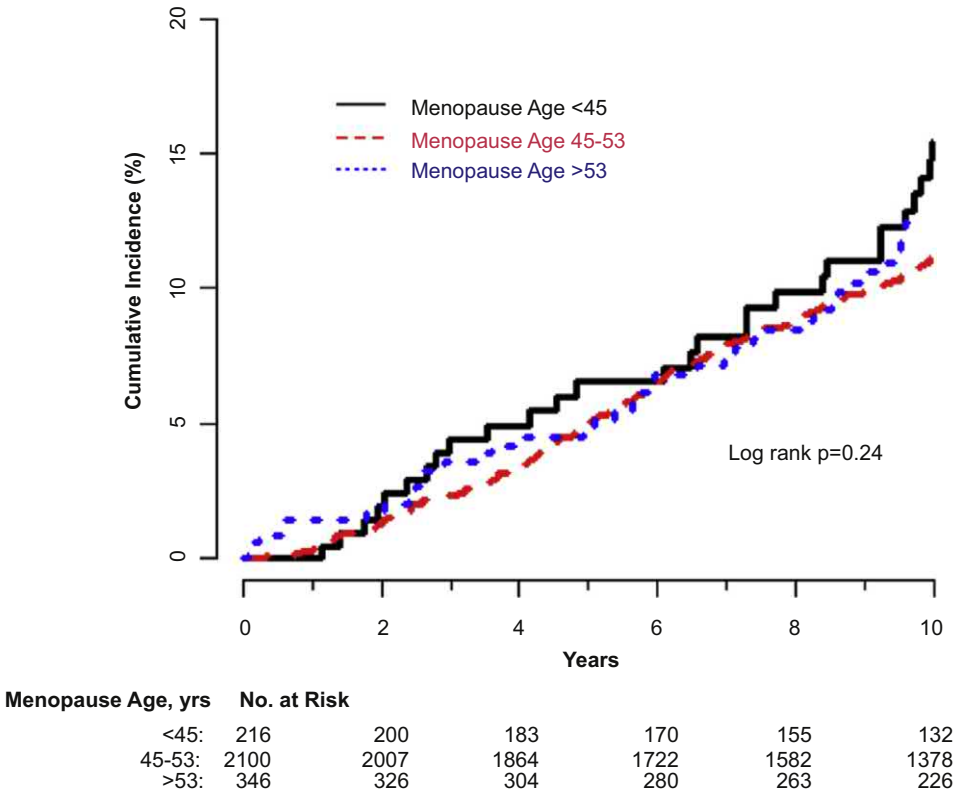

FIGURE 21.4 Cumulative incidence of atrial fibrillation, stratified by three categories of menopausal age: age <45, age 45–53, and age >53 years. Incidence of atrial fibrillation was similar irrespective of age of onset of menopause (long-rank test, $P = .24$). *Reproduced with permission Magnani JW. et al. Age of natural menopause and atrial fibrillation: the Framingham Heart Study. Am Heart J 2012;163(4):729–34.*

studies with a total number of 123,249 AF patients in a metaanalysis and demonstrated that obesity increased risk for AF by 49% [37]. The association between obesity and AF risk stems from the fact that obesity imposes greater hemodynamic stress on the heart in addition to its association with other AF risk factors such as diabetes, coronary artery disease, hypertension, and obstructive sleep apnea [37].

Azarbal et al. analyzed data from 81,317 postmenopausal women enrolled in the WHI observational study and demonstrated that increased physical activity and lower BMI were protective factors against the development of AF in postmenopausal women [40]. The reduction in AF risk correlated with the intensity of physical activity [40].

Obesity markers, such as, leptin, resistin, and adiponectin, have been associated with various cardiovascular effects [41–43]. Ermakov et al. demonstrated that serum resistin levels were significantly associated with incidence risk of AF in postmenopausal women [44]. The role of resistin in AF development is not entirely driven by obesity based on multivariable assessment models assessing the association between BMI and resistin levels [44]. One possible role for resistin in AF development is through systemic inflammation, which has been proposed to be a risk factor for AF [45]. Inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) have been associated with increased risk of AF [45–47]. Interestingly, resistin levels were found to be strongly correlated with levels of inflammatory markers such as CRP and IL-6 [48].

Statin therapy and AF incidence

Data from the Heart and Estrogen/progestin Replacement Study (HERS) trial demonstrated that statin therapy is associated with a reduced incidence and prevalence of AF in postmenopausal women with coronary artery disease [49]. Statin use was associated with a 55% reduction risk in AF incidence over a mean follow-up of 4.1 years [49]. Additionally, statin use was associated with 65% reduction in AF prevalence among all women included in the study [49].

Sex and AF management

Rate control versus rhythm control

The AFFIRM trial showed no significant difference in survival between rate-control and rhythm-control strategies

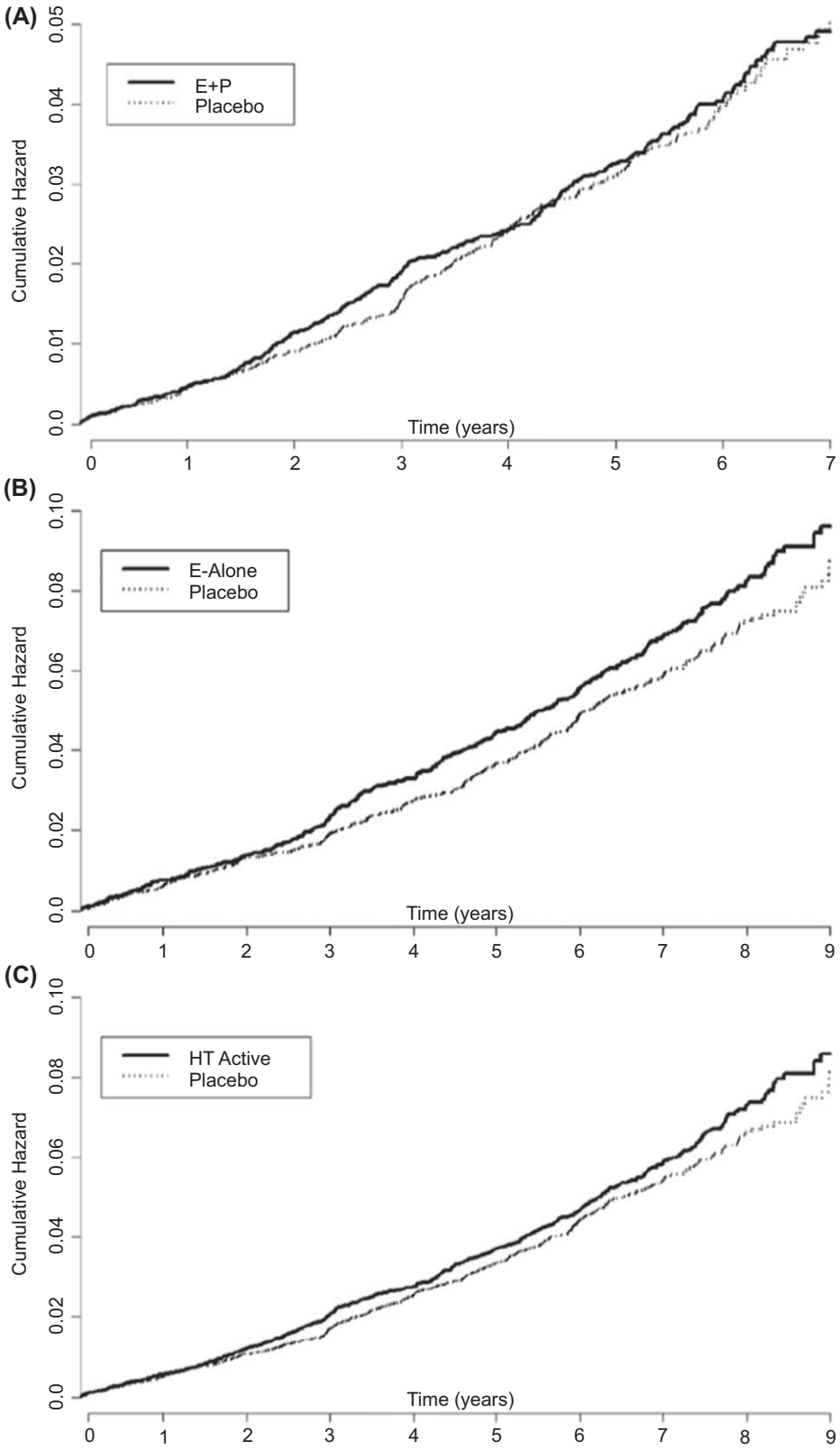

FIGURE 21.5 Cumulative incidences of atrial fibrillation in women in: the estrogen plus progestin (E + P) trial (A), the estrogen only (E alone) trial (B), and the combined hormone therapy trials (C). *Reproduced with permission Perez MV. et al. Effects of postmenopausal hormone therapy on incident atrial fibrillation: the Women's Health Initiative randomized controlled trials. Circ Arrhythm Electrophysiol 2012;5(6):1108–16.*

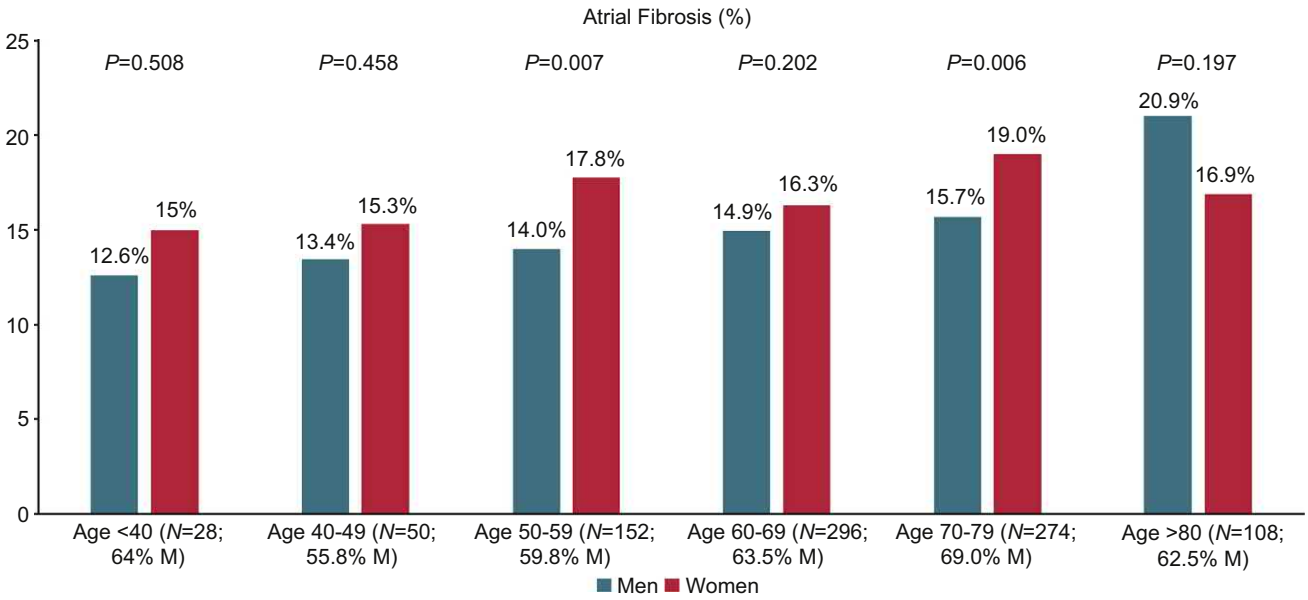

FIGURE 21.6 Left atrial fibrosis detected by LGE-MRI in men and women diagnosed with atrial fibrillation by age group. *Reproduced with permission Akoum N. et al. Age and sex differences in atrial fibrosis among patients with atrial fibrillation. Europace 2018;20(7):1086–92.*

for managing AF [50]. Female sex is associated with increased risk QT prolongation and Torsades de pointes and thus antiarrhythmic medications should be selected cautiously as some medications have been associated with increased risk for QT prolongation [51].

A subanalysis of the RACE trial revealed increased risk of cardiovascular morbidity and mortality in female patients (mean age 71 ± 8) who were treated with rhythm control. Female patients had greater incidence of Torsades de pointes with the use of class IA and III antiarrhythmics [52]. In addition, compared to rate-control strategies, female patients treated with rhythm control had more hospitalizations for heart failure and thromboembolic complications [52]. The risk of Torsades de pointes was doubled with the use of dofetilide [53]or sotalol but not with the use of amiodarone [15]. Female sex was associated with increased incidence of death in rhythm-control group compared to rate-control group in patients with persistent AF [54].

AF catheter ablation

AF catheter ablation success rate is similar among female and male patients [55,56]. Analysis of 21,091 patients (29% female patient with average age of 62 ± 11) who underwent AF ablation revealed significantly higher risk of early complications of hemorrhage and tamponade (Fig. 21.7) [56,57]. Long-term analysis demonstrated that female patients had higher rehospitalization rate for AF than male patients; however, female patients were less likely to undergo repeat ablation procedures or electrical cardioversion [57].

Anticoagulation

Despite some reports of lower prevalence of anticoagulant use in female AF patients compared to male patients [58–60], recent report from "The Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation" (GLORIA-AF) (n = 15,092, median age = 71.0 years, 45.5% female patients) revealed similar prevalence of anticoagulation use in male and female patients (Fig. 21.8) [61]. Interestingly, ATRIA trial showed a greater reduction in thromboembolism risk in female patients compared to male patients with warfarin anticoagulation. Risk of anticoagulation-related bleeding is controversial; some studies found no significant increase in anticoagulation-related risk of bleeding between male and female patients [30,33], whereas data from Canadian Registry of Atrial Fibrillation (CARAF) showed that women on warfarin had 3.35 times increased risk for an experiencing major bleed [59].

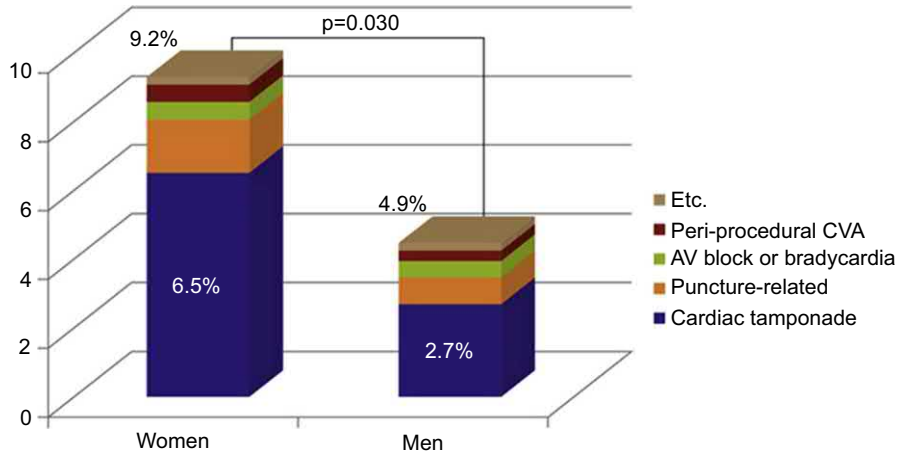

FIGURE 21.7 Increased incidence of procedure-related complications in women compared to men. *AV*, atrioventricular; *CVA*, cerebrovascular accident. *Reproduced with permission Roh SY. et al. Gender-related difference in clinical outcome of the patient with atrial fibrillation after radiofrequency catheter ablation. Korean Circ J 2018;48(7):605–18.*

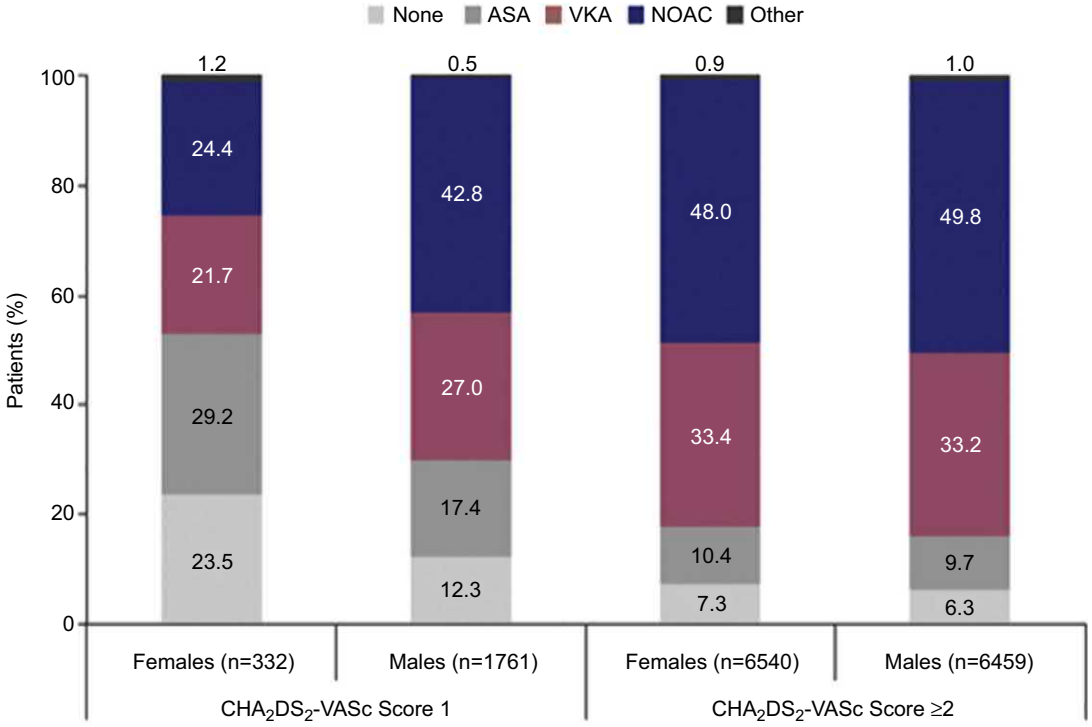

FIGURE 21.8 Sex differences in anticoagulation therapy prescription by stroke risk in GLORIA-AF Registry. *Reproduced with permission Mazurek M. et al. Gender differences in antithrombotic treatment for newly diagnosed atrial fibrillation: the GLORIA-AF Registry program. Am J Med 2018;131(8):945–955.e3.*

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Part VI

Channelopathies

Chapter 22

Congenital long-QT syndrome

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Sex differences in congenital long-QT syndromes

Long-QT syndromes (LQTSs) are the most common inherited cardiac channelopathies. LQTS are caused by genetic mutations in the main ion channels of ventricular myocytes. Affected patients have abnormally prolonged ventricular repolarization that can lead to early afterdepolarization and malignant ventricular arrhythmia [1−3]. LQTS are associated with a 1%−5% annual risk for life-threatening cardiac events (LTCEs) including syncope, seizure, aborted cardiac arrest, and sudden cardiac death. Even with the most contemporary and advanced therapy, nearly one in four patients who has sustained an LTCE is still at risk for another LTCE [4]. It has long been established that the QT duration is longer in women than in men [5]. Also known is that, in patients with LQTS, the longer the QT interval duration, the higher the risk for LTCEs [6,7]. Further, adult women with congenital LQTS are at increased risk for QT-related LTCEs [8]. In this chapter, we will begin with a brief review of the proposed mechanism of sex-related differences in baseline QT duration and the effects of sex hormones on cardiac repolarization. We will then discuss the role of sex differences in risk stratification for LTCEs, recurrence of LTCEs, and response to beta-blocker therapy. We will conclude with some recommendations for tailoring therapy to individual patients based on sex.

The effects of sex hormones on cardiac repolarization

Although evidence exists for age-specific sex hormone effects on ventricular cardiac repolarization, the complex interplay of sex hormones, age, and clinical outcomes is still incompletely defined. Clinical studies have shown QT shortening during the luteal phase of the menstrual period [9,10]. These observations suggest that progesterone may reverse an estrogen-induced QT prolongation effect. Consistent with that hypothesis is the increased risk for LTCEs found in women with LQTS during the postpartum period but not during pregnancy [11]. Animal studies have confirmed the presence of receptors for sex hormones in cardiac ventricular myocytes [12−15]. These studies concluded that estrogen could block I_{kr} current and prolong the ventricular repolarization duration and the QT interval at longer RR intervals [16]. Progesterone, in contrast, caused upregulation of the I_{ks} current and shortening of the ventricular repolarization duration and QT interval [14]. Testosterone, on the other hand, induced I_{kr} current increase and shortened ventricular repolarization and the QT interval [17]. There has not been enough evidence to support a genomically mediated effect of sex hormones on cardiac ventricular repolarization [18]. Female predominance cannot be explained by genetic transmission as the inheritance mode is mediated by autosomal mutant genes and not by sex-linked genes [19,20].

The role of sex differences in risk stratification throughout life (studies from the International Long-QT Registry)

The influence of sex on risk depends on the age group studied. Goldenberg et al. sought to determine risk factors for LTCEs in a cohort of children from the International Long-QT Registry [21]. The population included 3015 children (63% girls) who were followed from age 1 through 12 years. The mean QTc duration was significantly longer in girls than boys (493 ± 49 ms vs. 489 ± 48 ms, $P<.01$). As seen in Fig. 22.1A, LTCEs during childhood affected more boys than girls (57 [5%] boys versus 19 [1%] girls; $P<.001$). Boys with QTc >500 ms were at especially high risk, whereas QTc did not predict increased risk in girls. In fact, as seen in Fig. 22.1B, asymptomatic boys with QTc >500 had a 12-fold increase in the risk of LTCEs when compared to their counterpart females in this study. Syncope, especially within the preceding 2 years, was associated with increased risk of LTCEs in both boys and

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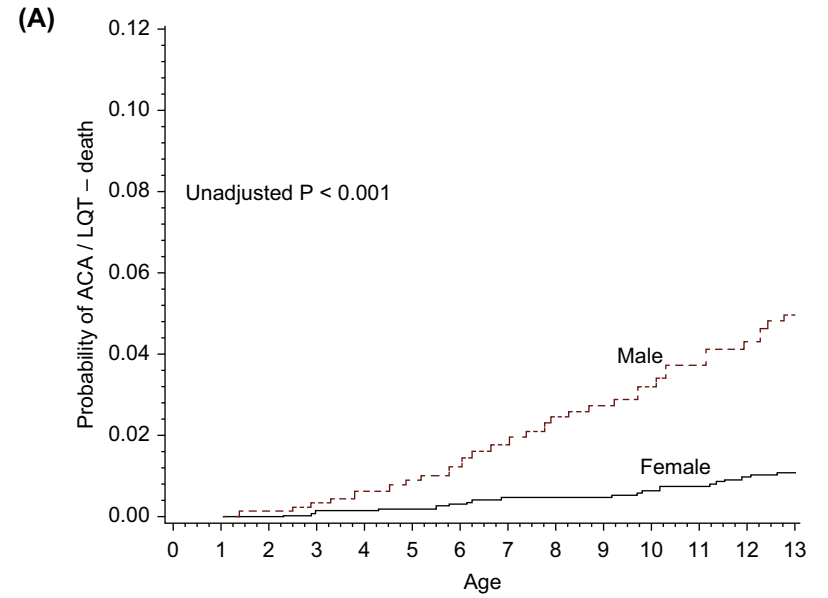
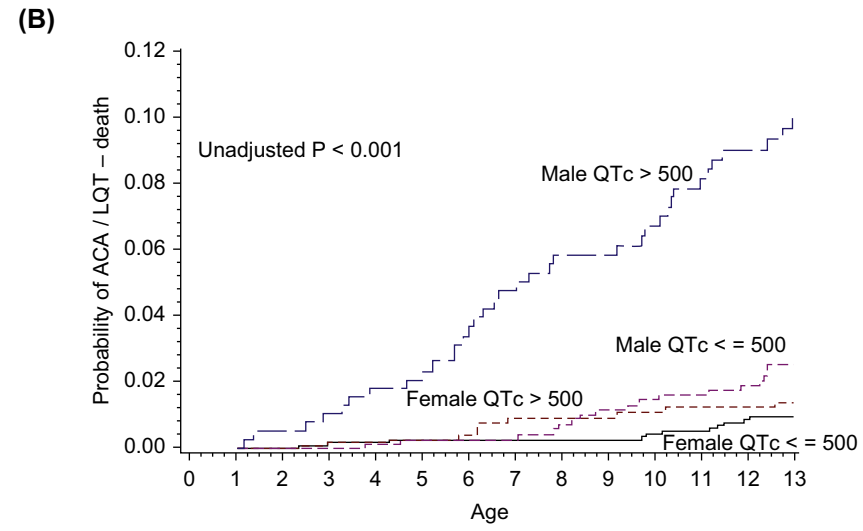


PATIENTS AT RISK

Male	1122	1104 (0.004)	1068 (0.014)	1009 (0.028)	897 (0.051)
Female	1893	1873 (0.002)	1836 (0.003)	1796 (0.005)	1714 (0.011)



PATIENTS AT RISK

Male QTc> 500	387	378 (0.01)	361 (0.034)	333 (0.059)	289 (0.10)
Male QTc< = 500	735	726 (0)	707 (0.003)	676 (0.011)	608 (0.025)
Female QTc> = 500	654	647 (0.002)	636 (0.005)	620 (0.009)	598 (0.014)
Male QTc< = 500	1239	1226 (0.002)	1200 (0.002)	1176 (0.002)	1116 (0.009)

FIGURE 22.1 Kaplan–Meier estimates of the probability of aborted cardiac arrest or sudden cardiac death by (A) sex and (B) sex and QTc subgroups (values in parentheses are event rates). *Reproduced from Goldenberg I, Moss AJ, Peterson DR, McNitt S, Zareba W, Andrews ML, et al. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. Circulation 2008;117(17):2184–2191 published with permission.*

girls. Beta-blocker therapy in this cohort was associated with significant reduction in LTCEs, particularly in the high-risk group.

Sauer et al. sought to determine predictors of LTCEs in 812 adults enrolled in the International Long-QT Registry [22]. The study included 428 patients with LQT1 (58% women), 302 patients with LQT2 (59% women), and 82 patients with LQT3 (51% women). Predictors of any cardiac event and of LTCEs were QT duration, prior cardiac events, LQT2 genotype, and female sex. Women had a risk

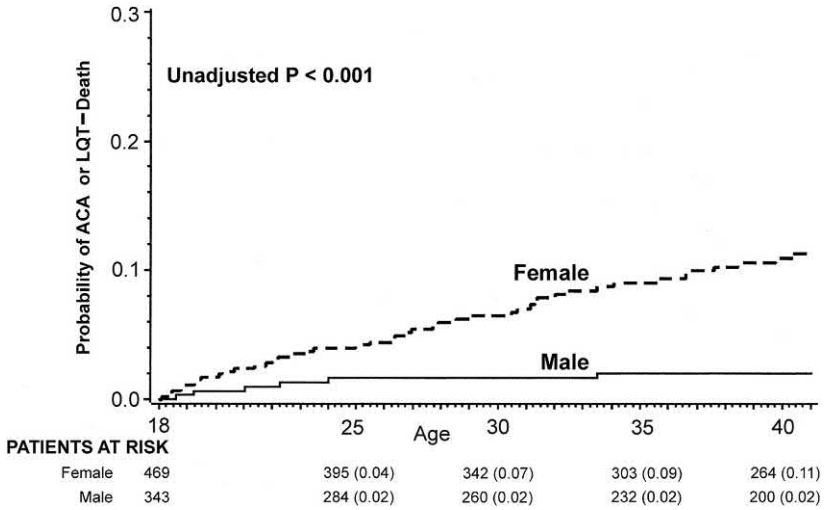


FIGURE 22.2 Kaplan−Meier estimate of the cumulative probability of any cardiac event (syncope/aborted cardiac arrest/LQTS-related sudden cardiac death) after age 18 years among mutation-carrying subjects on the basis of sex. *Reproduced from Sauer AJ, Moss AJ, McNitt S, Peterson DR, Zareba W, Robinson JL, et al. Long QT syndrome in adults. J Am Coll Cardiol 2007;49(3):329−337 with permission.*

of any cardiac event that was approximately threefold higher than men (Fig. 22.2). A similar increase in risk was seen for LTCEs.

Sex-related risk by genotype

LQT1 is the most common type of congenital LQTS [1]. It is caused by mutation in the KCNQ1 gene (11 P 15.5) causing a loss of function of the repolarization current I_{ks}. Contemporary data indicate that 37% of patients with LQT1 have experienced LTCEs at time of diagnosis [4], with an average age of 11 years at the time of the first event. Costa et al. investigated the risk of LTCEs from birth through age 40 years in a large population of 1051 genetically confirmed LQT1 subjects from 259 proband families [23]. The QTc interval duration was similar between males and females up to age 13 years. However, women had significantly longer QTc than men after age 13 (487 ± 56 ms female vs. 460 ± 53 ms male; $P < .001$). The LTCE rates were significantly higher among males than females during follow up, as seen in Fig. 22.3. No significant difference in syncopal events was found (35 female vs. 36 male; $P = .84$). Consistent with prior studies [8,24], LTCEs among males occurred mostly during childhood. By age 14, the cumulative probability for sudden cardiac death or aborted cardiac arrest was 10% among males in contrast

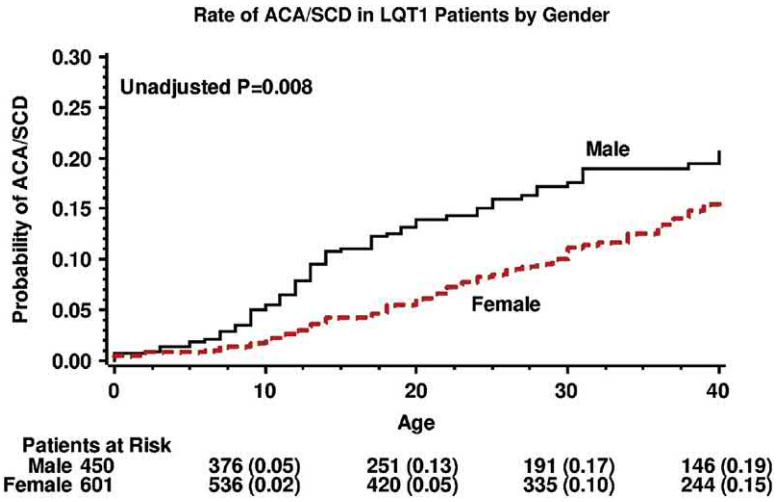


FIGURE 22.3 Kaplan−Meier estimates of the cumulative probability of aborted cardiac arrest or sudden cardiac death in patients with LQT1 by sex. *ACA*, aborted cardiac arrest; *LQT1*, long-QT syndrome type 1; *SCD*, sudden cardiac death. *Reproduced from Costa J, Lopes CM, Barsheshet A, Moss AJ, Migdalovich D, Ouellet G, et al. Combined assessment of sex- and mutation-specific information for risk stratification in type 1 long QT syndrome. Heart Rhythm 2012;9(6):892−898 with permission.*

to 3% among females. On the other hand, the cumulative probability of sudden cardiac death or aborted cardiac arrest after childhood and up to 40 years was higher in women than in men (19% vs. 15%). The risk of LTCEs was significantly higher in women with QTc > 500 ms and in men with QTc >550 ms. Interestingly, women with LQT1 mutation location in the membrane-spanning C-loop domain were at increased risk for sudden cardiac death and aborted cardiac arrest, in contrast to men, as seen in Fig. 22.4. This finding is of particular significance as it is plausible that the adrenergic-sensitive C-loop mutation makes women more vulnerable to LQT1-related arrhythmia at a lower level of exercise.

LQT2 is the second most common type of LQTS. LQT2 is caused by mutation in the KCNH2 gene (HERG on chromosome 79, location 35−36) causing loss of function of the repolarization current I_{kr}. About 39% of patients with LQT2 have already had an LTCE at the time of diagnosis, with an average age of 14 years at the time of the first LTCE [4].

Liu et al. [25] sought to explore risk factors for recurrent syncope and LTCEs in a cohort of 1648 patients from the International Long-QT Registry, with a focus on LQT1 and LQT2 genotypes. A total of 387 LQT1 patients and 257 LQT2 patients were included in the analysis. The findings were consistent with prior studies: LQT1 males were at higher risk for a first cardiac event during childhood and LQT2 females were at higher risk for a first cardiac event during adolescence. The risk of recurrent events during childhood was similar between female and male patients for both LQT1 and LQT2 genotypes. In contrast, the risk of recurrent events during adolescence was higher among female LQT2 patients.

In an analysis of risk for LTCE, Migdalovich et al. found a 26% lifelong probability of LTCE in women as compared to 14% in men (Fig. 22.5). While men with pore-loop mutations had increased risk relative to men with low-risk mutations (Fig. 22.6), women did not require the additional burden of a high-risk mutation to experience a high risk of LTCE (Fig. 22.7). [26].

LQT3 is the third most common type of LQTS. It is caused by a gain-of-function mutation in the sodium channel gene, SCN5A-encoded NAV1.5 sodium channel on chromosome 3 location 21−24. Women constitute about 55% of patients with LQT3 worldwide [27]. Priori et al. found that males with LQT3 genotype were at higher risk for LTCEs than their counterpart females [28]. Of note, most first events in this study occurred in childhood. In a larger study of LQT3 patients, females had a higher risk than males, especially during adulthood [27].

Wilde et al. studied 391 patients with LQT3 who were LTCE-free during the first year of life [27]. Subjects were enrolled from seven different international centers. A total of 217 (55%) patients were females. In all, 41 males (10%) and 77 females (20%) had experienced LTCEs at the time of enrollment. The probability of a first cardiac event was higher among females, markedly so in the age group range from 30 to 40 years. Interestingly, although the LQT3 patients showed the same sex cross-over during adolescence as LQT1 and LQT2 patients (i.e., boys had higher risk than girls, but women had higher risk than men), men with LQT3 had a significant residual risk during adulthood.

Sex differences in the response to beta-blocker therapy in congenital LQTS

Beta-blocker therapy is highly effective for the primary and secondary prevention of LTCEs in congenital LQTS in both males and females. The efficacy of beta-blockers in patients with LQT1 and LQT2 was investigated from birth to age 40 in a cohort of 971 patients from the International Long-QT Registry (549 LQT1 and 422 LQT2) [29]. The largest benefit was seen in the high-risk patients (boys and those with LQT1 during childhood, women and those with LQT2 during adulthood). A more modest benefit was seen in low-risk patients, probably because of their lower baseline event rate.

In the large LQT3 study by Wilde et al., beta-blocker therapy was used for 111 (29%) patients (51 males and 60 females) who were followed for an average of 87 months posttreatment. In marked contrast to prior studies [30,31], beta-blocker therapy significantly reduced the risk of LTCEs in female LQT3 patients by 83% but only insignificantly in male patients. The highest risk of LTCEs in this study was seen in female patients who were never treated with beta-blockers and in whom QTc interval was over 500 ms. There was no evidence of harm or proarrhythmic effect from beta-blocker therapy [27].

Pregnancy and menopause

Seth et al. [11] studied the effect of pregnancy on LQTS patients in a cohort of females enrolled in the International Long-QT Registry. While the risk of cardiac events was reduced during pregnancy, the risk was substantially elevated, 2.7-fold, during the postpartum period. The risk for LTCEs was 4.1-fold higher during the first 9 months postpartum when compared to the preconception time period. The highest risk was seen among women with LQT2. Beta-blocker therapy significantly reduced this risk.

Buber et al. [32] studied 282 women (151 LQT1 and 131 LQT2) before and after menopause. LQT2 women had an increase in cardiac events, primarily syncope, during the

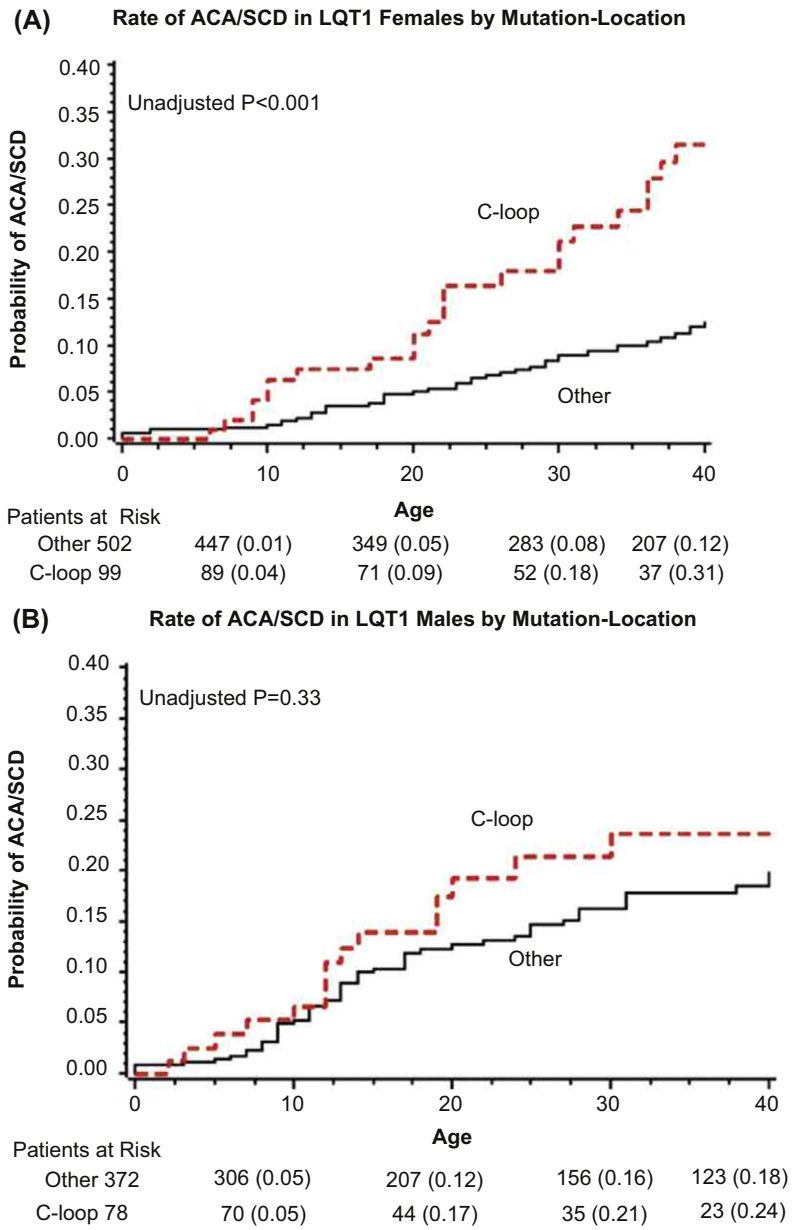


FIGURE 22.4 Kaplan–Meier estimates of the cumulative probability of aborted cardiac arrest or sudden cardiac death in (A) women with LQT1 and (B) men with LQT1, by mutation location. *ACA*, aborted cardiac arrest; *C-loop mutations*, cytoplasmic-loop mutations; *LQT1*, long-QT syndrome type 1; *SCD*, sudden cardiac death. *Reproduced from Costa J, Lopes CM, Barsheshet A, Moss AJ, Migdalovich D, Ouellet G, et al. Combined assessment of sex- and mutation-specific information for risk stratification in type 1 long QT syndrome. Heart Rhythm 2012;9(6):892–898 with permission.*

transition to menopause and during the postmenopausal period. In contrast, LQT1 women experienced a decreased risk of syncope at the time of menopause.

International Long-QT Registry data compared with a more contemporary data set

Analyses performed on data from the International Long-QT Registry consistently showed a higher risk of cardiac events among boys than girls, a relationship which crossed over during adolescence, with women having a higher risk than men throughout adult life. Boys with LQT1 and adult women with LQT2 had particularly high risk. It should be noted that the International Long-QT Registry contains both contemporary and historic data, and many of the earlier patients were untreated. Also, several generations ago, boys tended to be more active than girls during childhood. Against this backdrop, the recent study by Shimizu et al. [33] is particularly interesting. Shimizu analyzed data from 1124 Japanese patients (521 LQT1, 487

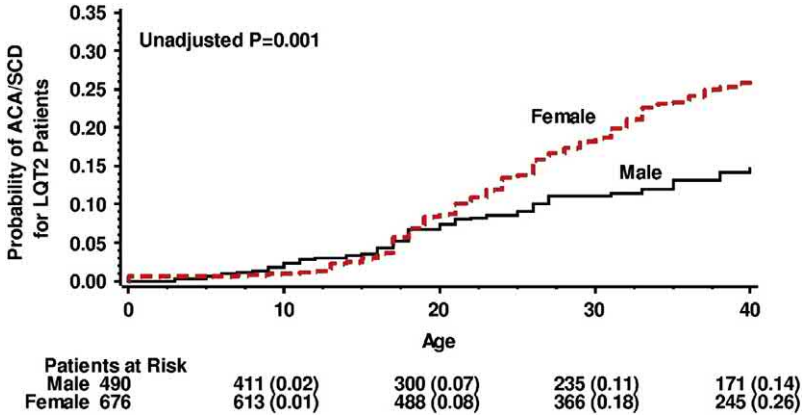


FIGURE 22.5 Kaplan–Meier estimates of the cumulative probability of aborted cardiac arrest or sudden cardiac death in LQT2 patients by sex. *ACA*, aborted cardiac arrest; *LQT2*, long-QT syndrome type 2; *SCD*, sudden cardiac death. *Reproduced from Migdalovich D, Moss AJ, Lopes CM, Costa J, Ouellet G, Barsheshet A, et al. Mutation and gender-specific risk in type 2 long QT syndrome: implications for risk stratification for life-threatening cardiac events in patients with long QT syndrome. Heart Rhythm 2011;8(10):1537–1543 with permission.*

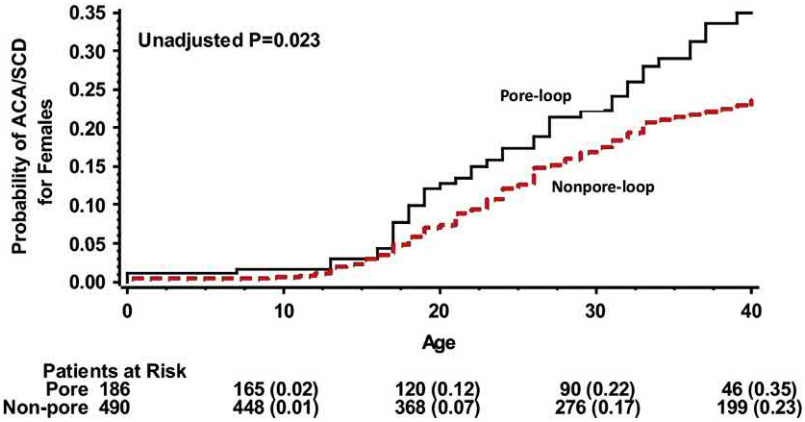


FIGURE 22.6 Kaplan–Meier estimates of the cumulative probability of aborted cardiac arrest or sudden cardiac death in LQT2 women by mutation location. *ACA*, aborted cardiac arrest; *LQT2*, long-QT syndrome type 2; *SCD*, sudden cardiac death. *Reproduced from Migdalovich D, Moss AJ, Lopes CM, Costa J, Ouellet G, Barsheshet A, et al. Mutation and gender-specific risk in type 2 long QT syndrome: implications for risk stratification for life-threatening cardiac events in patients with long QT syndrome. Heart Rhythm 2011;8(10):1537–1543 with permission.*

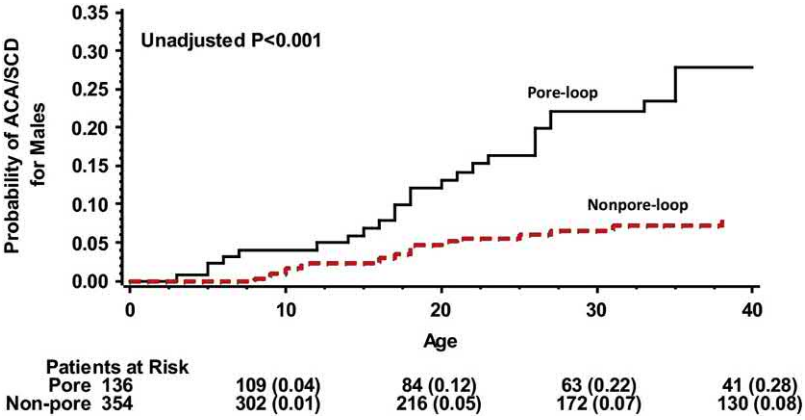


FIGURE 22.7 Kaplan–Meier estimates of the cumulative probability of a first aborted cardiac arrest or sudden cardiac death in LQT2 males by mutation location. *ACA*, aborted cardiac arrest; *LQT2*, long-QT syndrome type 2; *SCD*, sudden cardiac death. *Reproduced from Migdalovich D, Moss AJ, Lopes CM, Costa J, Ouellet G, Barsheshet A, et al. Mutation and gender-specific risk in type 2 long QT syndrome: implications for risk stratification for life-threatening cardiac events in patients with long QT syndrome. Heart Rhythm 2011;8(10):1537–1543 with permission.*

LQT2, 116 LQT3) diagnosed between 2006 and 2013. Similar to the International Long-QT Registry findings, LQT1 events were more likely to occur in childhood and LQT2 events occurred more after adolescence. In contrast to the International Long-QT Registry findings, no sex difference was seen prior to puberty in patients with LQT1, LQT2, or LQT3. After puberty, risk was higher in women than men among LQT1 patients, markedly higher in women than men among LQT2 patients, and equivalent in men and women among LQT3 patients. One can speculate that the lack of sex differences in childhood might reflect contemporary treatment and/or a similar access to exercise among boys and girls. Possibly, the lack of sex difference among adults with LQT3 might reflect the small sample size or short duration of follow-up.

Concluding thoughts

How, then should the clinician think about the management of LQTS in males versus females? The studies summarized above consistently show certain high-risk markers. In all individuals, male or female, longer duration of the QT interval is associated with higher risk. A history of syncope, particularly recent syncope, with features consistent with arrhythmic etiology, is a powerful predictor of risk in both men and women. As a first syncopal event may occur during childhood, adolescence, or young adulthood, individuals in these age ranges may have yet to manifest their symptoms. This is particularly true in females, whose QT prolongs during adolescence. As we have seen, women with LQT2 have an especially high risk, especially in the postpartum period. These facts should inform our integration of established guidelines into clinical care.

The 2017 AHA/ACC/HRS guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death [34] state that a beta-blocker is recommended with a resting QTc $>$ 470 ms (Class I recommendation) and that beta-blocker therapy is reasonable in asymptomatic patients with QTc $<$ 470 ms (Class IIa). Further, in high-risk individuals, including those with persistent symptoms and/or other high-risk features (Class I), and in asymptomatic patients with QTc $>$ 500 ms (Class IIb), intensification of therapy with medication, left cardiac sympathetic denervation, and/or an implantable cardioverter-defibrillator are recommended. These guidelines, appropriately, give room for therapy individualization. We would assert that sex, age, and genotype should be considered, as described in the examples below.

A 40-year-old man with no history of symptoms, with LQTS diagnosed through family screening, and with QTc $<$ 470 ms, has no high-risk features and is unlikely to develop the onset of LQTS arrhythmias in the absence of new provoking circumstances (such as addition of QT-prolonging medication or severe electrolyte disturbance). It would be reasonable not to treat this patient with chronic beta-blocker therapy. In contrast, his 13-year-old daughter, also asymptomatic and diagnosed through family screening, with QTc $<$ 470 ms, has not yet lived through adolescence and early adulthood, and she may be at higher risk for LQTS arrhythmic events, particularly if she has the LQT2 genotype. Thus, it would be reasonable for her to initiate beta-blocker therapy.

An asymptomatic man with QTc of 510 ms and LQT1 is likely to experience a high degree of protection from beta-blocker therapy alone. In contrast, an asymptomatic woman with QTc of 510 ms and LQT2 will have substantial residual risk on beta-blocker therapy alone. In her case, strong consideration should be given to the addition of an implantable cardioverter-defibrillator.

Contemporary treatment offers patients with LQTS an excellent outlook. Adequate life-protecting therapy must be balanced against overtreatment, which may diminish quality of life. Since sex affects prognosis, sex must be considered during management decisions.

Important points

- During adolescence, complex hormonal influences result in longer QT intervals in women than in men.
- International Long-QT Registry data show that boys have a higher arrhythmic risk than girls, prior to adolescence. However, a recent study of contemporary patients in Japan did not find a higher risk in boys.
- Adult women with congenital LQTS have higher arrhythmic risk than men. The arrhythmic risk is especially high in women with long QT type 2 and during the postpartum period.
- In both males and females, longer QT duration and history of syncope are predictors of arrhythmic risk.
- In both males and females, antiadrenergic therapy reduces the risk of arrhythmic events.

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Chapter 23

Congenital short-QT syndrome

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Material

In early 1999, the first family with short QT and atrial fibrillation was discovered in the United States (Fig. 23.1) and published in 2000 [1] together with the history of an adult female in Spain with similar short QT, who had died suddenly. Prior to these events, short QT had not been considered a risk factor for neither atrial fibrillation nor sudden cardiac death, but comparisons were immediately made with long-QT syndrome (LQTS), which had been known since 1957 [2], and a new disease called short-QT syndrome (SQTS) was contemplated. Eighteen years later in 1975, Schwartz et al. [3] gave a comprehensive description of all known cases of LQTS, some of them in a last minute addendum. The total number of patients with LQTS at that time was 220. Now, 18 years after the discovery of SQTS, the total number of published patients with this syndrome is 234, suggesting that the prevalence of the two syndromes may be identical and therefore a comparison of the two syndromes is feasible (Table 23.1). New cases of SQTS representing 144 families have been presented in 48 articles [1,4–50]. Twenty-four papers are single case reports and 10 are single family reports thatinclude the largest family with 23 carriers of the mutated gene (*SLC4A3*). A combined 93 SQTS patients have been presented in two multicenter studies by Giustetto et al. [24] (20 patients) and by Mazzanti et al. [39] (73 patients).

Some of the articles describing patients with SQTS (unfortunately, many with the highest number of SQTS patients) do not include age, sex, QT-interval duration, and the HR of individual patients, or, in a few cases, they fail to identify the status of patients as new or those previously published. For instance, in the case report of a 13-year-old child with SQTS by Villafane et al. [19,] nine additional patients less than 20 years of age were mentioned in the discussion section of the paper without any clear indication of their status as either new or previously published patients. Since the article was presented as a case report, only the 13-year-old child could therefore be counted as a new patient in this presentation. Likewise, from the study by Watanabe et al. [22], 12 patients with SQTS either referred to their institution or from previous reports and therefore cannot be included due to lack of more precise individual patient data. In the study by Giustetto et al. [24], 20 new SQTS patients also did not have enough individual patient data to be fully included. Some observations from this study are, however, important and will be included. An international case series involving 21 patients from 15 centers by Villafane et al. [31] describes a combination of new and previously published patients without individual patient data and can therefore not be included in the discussion of sex differences. These four articles represent several patients with SQTS who are not eligible for inclusion in our discussion of sex differences, leaving 222 for further consideration. Among them is the large series of new SQTS patients by Mazzanti et al. [39] In this study of 73 SQTS patients from 47 families, several important points were touched upon, but individual patient data are missing. This study and the study by Giustetto et al. [24] will therefore be presented separately, leaving a total of 144 patients as **the core study group** applicable for a collective discussion of sex and age relationships based upon the presence of individual personal data. Among them there are, however, 11 patients where information about age is missing, one where sex is missing and 23 where either QT or QTc is missing together with HR. Such patients will be included in situations where the missing data are inconsequential, explaining why the number of patients included in various calculations may vary slightly.

Because of the low number of known SQTS patients, emerging patterns worthy of a discussion will, in some cases, have to serve as replacements for more categorical statements backed by statistical calculations. Special attention will be made to the emerging evidence, both in laboratory testing and clinical studies, of a connection between testosterone and QT-interval duration and how it may explain some of the clinical observations regarding sex differences in SQTS.

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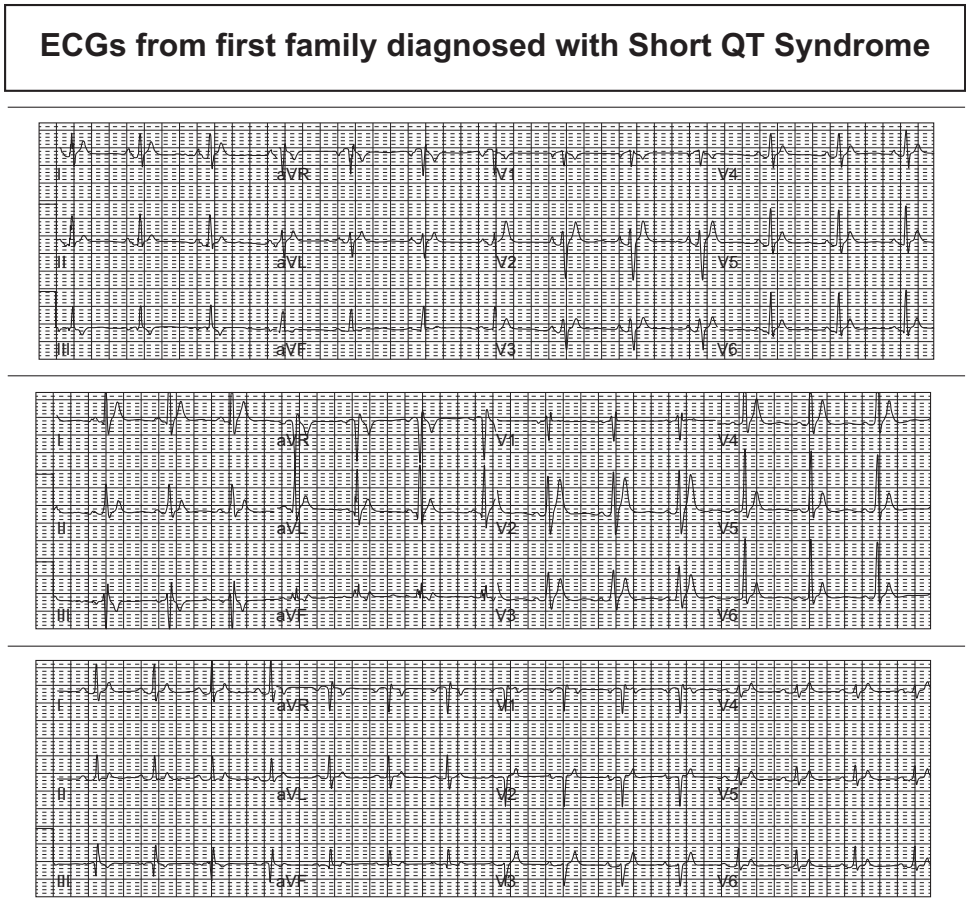

FIGURE 23.1 ECGs from first family diagnosed with Short-QT Syndrome.

TABLE 23.1 Comparison at 18 years of follow-up of LQTS verses SQTS.

	Long-QT syndrome	Short-QT syndrome
Year of discovery	1957	2000
Year of major review	1975	2018
Years of follow-up	18	18
Number of papers	61	49
Number of case reports	14	24
Total number of patients	220	234
Number of sex designated patients	203	202
Male sex (number (%))	89 (44)	142 (70)
Female sex (number (%))	114 (56)	60 (30)

Sex differences in the QT-interval duration

Looking at the evolution of our understanding of sex differences in QT-interval duration between patients with LQTS and people with normal QT helps understand the same phenomena in patients with SQTS. Eighteen years after the syndrome was discovered, the first review of a larger group of patients with LQTS by Schwartz et al. [3] (1975) suggested an inclination of a sex difference in the prevalence of LQTS favoring females. Out of 203 LQTS patients, 56% were females. To investigate sex differences in the QT interval in healthy people according to age, Rautaharju et al. [51] (1992) studied the ECGs from a community-based representative North American population sample of 14,379 children and adults aged from birth to 75 years of age. The principal finding was significantly longer QT interval values in females in all age groups between 15 and 50 years. This difference was due to a *20 ms drop in rate-corrected QT values in adolescent males after puberty*, whereas *QT values of females remained constant from birth to old age*. This age- and sex-related difference in QT interval duration seen in healthy individuals was later found to exist in families with genotyped LQTS (Lehmann et al. [52]). In familial LQTS linked to either chromosome 7q or 11p, men were found to exhibit shorter mean QTc values than women from both genotype-positive patients and their genotype-negative blood relatives. In the analysis of data from the International LQTS Registry (Locati et al. [53]), out of 479 probands, 70% were females and out of 1041 affected family members with QTc $>$ 440 ms, 58% were females. *This sex-related difference in prevalence of patients with LQTS was not seen when LQTS gene carriers were looked at separately*. Out of the 162 LQTS gene carriers, only 54% were females (p = NS). Men with LQTS were again found to exhibit shorter mean QTc values than women with a corresponding risk of cardiac events higher in females than in males. Since the unbalanced sex distribution could not be accounted for by genetic transmission, *a possible role of androgens was suggested for the first time*. Further indirect evidence of a relationship between testosterone and the duration of the QT interval in men was presented by Bidoggia et al. [54] who measured JTc (as a surrogate for QTc) in 27 orchiectomized men comparing it to JTc in 53 nonorchiectomized men. The finding was a loss of male ECG pattern and significantly longer JTc's in the orchiectomized men than in the nonorchiectomized men. In this study, testosterone levels were not measured but assumed to be highest in the nonorchiectomized men. The impression from the study was that testosterone plays an important role in modulating cardiac repolarization.

Relationship between QT-interval duration and testosterone

Several later studies further exposed a relationship between the QT interval and testosterone in patch-clamp studies of testosterone; in studies of serum testosterone and QT intervals in large, general population cohorts; and in testosterone treatment studies.

1. Patch-clamp studies of testosterone

A plausible mechanism for the effects of testosterone on ventricular repolarization in men was demonstrated by Bai et al. [55] when they examined the effects of testosterone on action potential duration (APD) and membrane currents in isolated guinea pig ventricular myocytes using patch-clamp technique. They showed that *testosterone rapidly shortens APD*, with an EC_{50} of 2.1−8.7 nmol/L, which is within the limits of physiological testosterone levels in men. The APD shortening was found to be *due to enhancement of slowly activating delayed rectifier K^+ currents (I_{Ks}) and suppression of L-type Ca^{2+} currents ($I_{Ca,L}$)*. In 2008, Ridley et al. [56] using whole-cell patch-clamp measurements of I_{hERG} in human neuroblastoma cells added various concentrations of testosterone solution, demonstrating for the first time that *testosterone can stimulate hERG K^+ channels* via *activation of classical androgen receptors*. As hERG channel function is pivotal to normal ventricular repolarization in the heart, the findings of the study raised the possibility that acute or chronic modulation of I_{hERG} by testosterone may contribute to known sex differences in cardiac repolarization.

2. S-testosterone and QT interval in large general population cohorts

In 2010, van Noord et al. [57] studied testosterone levels and QTc (Bazett's formula) in 445 males (≥55 years) from a Rotterdam study cohort and 1428 males from Study of Health in Pomerania. The study showed an *association of serum testosterone with shortening of the QTc interval and prolongation of the RR interval in men*. Zhang et al. [58] (2011) studied QT and endogenous testosterone levels in 727 men enrolled in Third National Health and Nutrition Examination Survey. They were able to confirm an inverse association between testosterone levels and the QTc interval and agreed that differences in testosterone levels were the likely explanation for the differences in QTc between males and females.

3. Testosterone treatment studies

Charbit et al. [59] showed the effect of a single injection of testosterone on QTc in 11 hypogonadal men. They found significantly shorter QTc in patients who had high endogenous testosterone levels compared to those with low levels after the injection. Giraldi et al. [60] measured QTc (Bazett's formula) in 26 men with hypogonadism before and after testosterone therapy, compared to 26 age-matched controls. A higher prevalence of prolonged QTc was found in hypogonadal men than in controls, with shortening and normalization of prolonged QTc after testosterone therapy. Jørgensen et al. [61] did a case−control study of 62 males

with Klinefelter syndrome and 62 healthy males matched on age. Forty-one patients with Klinefelter syndrome underwent treatment with testosterone in a nonrandomized fashion either as intramuscular injections or transdermal application. The comparison of the QTc intervals in the three groups showed testosterone treated males with Klinefelter syndrome (QTc mean 358 ms) to be the shortest, while untreated and thus hypogonadal patients with Klinefelter syndrome had a QTc comparable to controls (QTc mean 379 ms).

Sex differences in SQTS

From these studies, it is evident that testosterone plays a major role in the difference in QT interval duration between men and women by shortening the QT intervals in men. The effect of progesterone and estrogen on the QT interval in humans appears to be minimal and unlikely to play any significant role in the QT interval difference between men and women (Sedlak et al. [62]). In the absence of definite sex-specific criteria for QT duration, it has been suggested that such differences may induce a bias, favoring LQTS diagnosis among adult females. Looking at SQTS, it might also be used as an argument in favor of an SQTS diagnosis among adult males. In the first review of SQTS in 2006 (Giustetto et al. [12]), out of 29 patients with a median age of 30 years, 21 (72%) were males, while in a later multicenter study by Mazzanti A et al. [39], out of 73 patients with SQTS, 61 (84%) were male. When the diagnosis in this study was made on the basis of clinical parameters, excluding the contribution of genetic testing, the predominance of male patients was as high as 91%. Among all 221 SQTS patients in the literature with sex designation, 70% were male, and in our core study group of 129 SQTS patients with complete individual data, 58% were male. Fig. 23.2 clearly shows that the age when most males are detected with SQTS is between puberty and old age when the circulating level of testosterone is the highest and the QT intervals possibly the lowest, while there does not seem to be any preferential age for detection of SQTS in females.

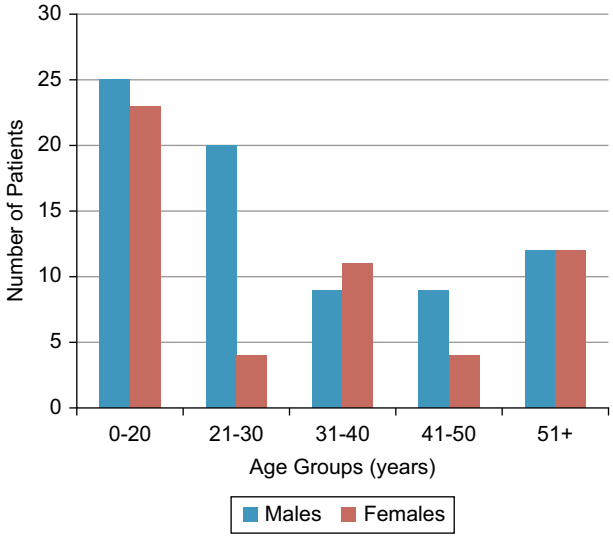

FIGURE 23.2 Distribution of 129 SQTS patients by sex and age.

Genetic mutations and sex

This dominance of male sex seen in a non−sex-linked hereditary disease with 100% penetrance as SQTS was, as expected, not present when only genotype-positive patients were examined. In the study by Mazzanti et al. [39], there was an even distribution of males and females among genotype-positive patients, while in genotype-negative patients, 91% were males. In our core study group, out of 93 genotype-positive patients, there were 48 males and 45 females (p = NS) (Table 23.2), while out of the 25 genotype-negative patients, 21 or 84% were males. In the remaining 17 patients who were not genotyped, 11 or 65% were males. Among the 21 patients who were genotype-negative, in 13 from 5 families, the disease in each family was based on a history of SCD and a short QT interval. It is therefore evident that when the diagnosis of SQTS is established on the basis of clinical parameters with either no genetic testing or a negative genetic testing, the predominance of male patients is overwhelming. A question could therefore be raised regarding the validity of the diagnosis of SQTS in some of the nongenotyped or genotype-negative males. If QTc was different in this group, than in genotype-positive males such a suspicion could be valid, and such a difference was actually seen in the study by Mazzanti et al. [39,] where the QTc intervals from 61 patients with complete genetic screening, the QTc intervals were found to be significantly shorter in mutation carriers verses non-carriers ($P = .002$). In the core study group, no such difference was detected, but the method used for measurement of the QT interval in this study group was not standardized and therefore not suited for detection of minor differences in QT interval. It is still possible, as previously mentioned, that

TABLE 23.2 Distribution of 129 patients by sex and age at 10 year increments.

Age group in years	Males	Females
0−10	6 (27%)	16 (73%)
11−20	19(73%)	7 (27%)
21−30	20 (83%)	4 (17%)
31−40	9 (45%)	11 (55%)
41−50	9 (69%)	4 (31%)
51−60	5 (50%)	5 (50%)
60+	7 (50%)	7 (50%)
TOTAL	75 (58%)	54 (42%)
11−50	57 (69%)	26 (31%)

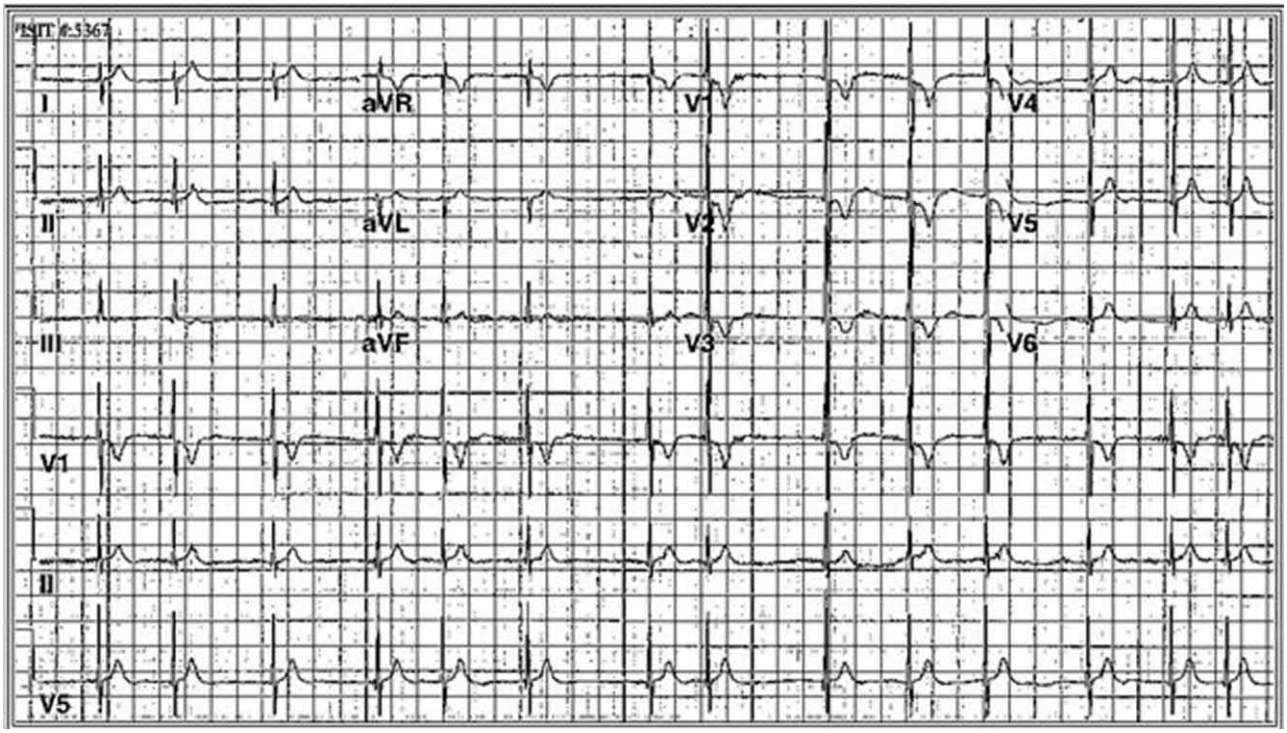

FIGURE 23.3 12-lead ECG at 25 mm/s from newborn girl with atrial fibrillation in the setting of SQTS. QT/QTc = 240 ms/287 ms

the absence of definite sex-specific criteria for QT duration may induce a bias, favoring an SQTS diagnosis among adult males who have shorter QT interval than females and at the same time a risk of missing the clinical diagnosis in some adult females without or negative genotyping. In a very comprehensive study by Imboden et al. [63] of possible causes for the female predominance in LQTS, they claimed to have found compelling evidence of an unbalanced transmission of deleterious alleles causing some forms of LQTS. Such an explanation is not likely in SQTS, however, where there is no sex difference in the prevalence of SQTS in gene carriers.

Sex and SQTS in children

A short QT interval is often undetected at birth or early childhood because of the rare occurrence of an ECG being recorded in this age group and due to the difficulty of making the diagnosis of a short QT interval during tachycardia. Looking at the percent distribution of 129 patients by sex and age, there is an even distribution of male and female from newborn till 20 years of age (Fig. 23.2). In our core study group, there were 21 children $\leq$10 years of age. Fourteen (66%) were females and seven (34%) males. Shared among them was a special form of SQTS due to a *KCNQ1-V141M* mutation, often diagnosed in early childhood because of the presence of severe bradycardia often accompanied by atrial fibrillation (Fig. 23.3). To date, this is the most frequent mutation in SQTS patients with an especially strong female predominance. Out of 10 patients with this syndrome in 9 families, 8 have been female. The clinical manifestations were fetal bradycardia in seven, bradycardia at birth in two, and slow atrial fibrillation at the age of 3 years old in one. All 10 patients ended up in persistent atrial fibrillation. Of the additional 11 children diagnosed with SQTS, a *KCNH2* mutation was seen in 4, and a *KCNJ2* mutation in 1. One child was negative and three children were not genotyped. An interesting observation was presented by Villafane et al. [19] in an article about a 13-year-old boy with aborted SCD in the setting of a QT interval of 300 ms and a QTc of 319 ms. In the article, additional data from nine pediatric patients (age 7–19 years old) diagnosed with SQTS were included. According to the authors, it was a biased sampling where all were either symptomatic or had a family history of SCD or SQTS. Lacking important information, they were not included in our core study group (vide supra). None of them were genotyped, but all were male.

Sex and incidence of SCD in patients with SQTS

SCD is the dominant symptom in all publications of SQTS, either as the presenting symptom in a new patient or as part of the family history of a new patient. In our core study group of 70 families where sex designation was available, SCD or family history of SCD presumed to be due to SQTS was present in 43 or 61% of probands (Tables 23.3 and 23.4). Out of 45 males, SCD or history of SCD was the presenting symptom in 64%, while out of 25 females, it was

TABLE 23.3 Reason for referral of 117 probands of families with SQTS.

Reason for referral	Cor study group		Mazzanti et al. [39]	Cor study group + Mazzanti et al. [39]
	Number (%) of Males	Number (%) of Females	Number of Patients	Number of Patients
SCD/ab SCD	17	10	19	46
Incidental finding of short QT	6	2	17	25
Family history of SCD	9	3	2	14
Syncope	1	1	9	11
Syncope in a family hx of SCD	3	1	0	4
Palpitations/ventricular tachycardia	1	0	0	1
AF/severe bradycardia at young age	8	8	0	16
TOTAL	45(64%)	25(36%)	47	117

TABLE 23.4 Description of 23 different causative *cation* channel gene mutations in 8 different genes from 45 index patients out of 105 SQTS families who have been genetically tested, in addition to a single *anion* exchanger gene mutation found in 27 individuals out of 49 from 2 other SQTS families tested.

References to the original description of SQTS mutation	*GENE* locus	Nucleotide change	Amino acid change	Number of families	Number of patients	
Short-QT syndrome *Cation channel genes*					Male	Female
Brugada et al. [5]	***KCNH2***	c1764a/ c1764g	N588K	6	5	7
Sun et al. [23]	7q36.1	c1853t	T618I	8	9	10
Redpath CJ. et al. [18]			E50D	1	1	0
Harrell et al. [40]		c1679T > C	I560T	1	1	0
Akdis et al. [50]		c1691T > G		1	1	2
Wakatsuki et al. [49]			W927G	1	1	0
Bellocq et al. [6]	***KCNQ1***	g919c	V307L	1	1	0
Hong et al. [11]	11p15.5		V141M	9	3	7
Rhodes et al. [64]			I274V	1 (SIDS)	?	?
Moreno et al. [41]		t127910a	F279I	1	1	0
Mazzanti et al. [39]			R259H	1	?	?
Rothenberg et al. [46]		c859G > A	A287T	1	0	1
Priori et al. [9]	***KCNJ2***	g514a	D172N	2	1	1
Hattori et al. [27]	17q24.3		M301K	1	0	1
Deo et al. [32]		a896t	E299V	2	1	0
Ambrosini et al. [37]			K346T	1	2	0

Continued

TABLE 23.4 Description of 23 different causative *cation* channel gene mutations in 8 different genes from 45 index patients out of 105 SQTS families who have been genetically tested, in addition to a single *anion* exchanger gene mutation found in 27 individuals out of 49 from 2 other SQTS families tested.—cont'd

References to the original description of SQTS mutation	*GENE* locus	Nucleotide change	Amino acid change	Number of families	Number of patients	
Brugada syndrome with short QT interval ***Cation channel genes***						
Antzelevitch et al. [14]	***CACNA1C***	c116t	A39V	1	1	0
Antzelevitch et al. [14]	12p13.3	a1468g	G490R	1	1	0
Mazzanti et al. [39]			R1977Q	1	?	?
Antzelevitch et al. [14]	***CACNB2b*** 10p12.33	c1442t	S481L	1	3	3
Templin et al. [25]	***CACNA2D1*** 7q21.11	c2264g	S755T	1	0	1
Itoh H. et al. [20]	***KCNH2*** 7q36.1		R1135H	1	1	0
Hong et al. [29]	***SCN5A*** 3p21	g2066a	R689H	1	1	0
Short-QT syndrome ***Anion exchanger gene***						
Thorsen et al. [48]	***SLC4A3*** 2q35	c1109G > A	R370H	2	16	12
	Total:	47	48	45		

? indicates lack of information.

the presenting symptom in 56% (p = NS) Mazzanti et al. [39]. A similar study of 47 families with SQTS likewise found very little difference in the percentage of males and females with life-threatening arrhythmias and pointed out *"just because we see more male than female patients with SQTS in our clinic, we should not consider affected female patients at a lower risk of cardiac arrest."* In addition it was stated that female patients presenting with a short QT interval have a risk of experiencing cardiac arrest similar to that of male patients.

Summary

SQTS is a rare disease more commonly diagnosed in men than in women, but with similar risk for SCD in males and females and a prevalence compatible to that of LQTS. The prevalence of sex-related differences in both diseases indicates women are predominantly affected with LQTS and men are predominantly affected with SQTS, both likely due to shorter QT in men than in women, likely secondary to high testosterone blood levels in men after puberty. *The longer QT in women may favor a diagnosis of LQTS, while the shorter QT in men will favor SQTS, especially in the absence of definite sex-specific criteria for QT duration in both syndromes*. An unanswered question for both diseases is, however, why we only see these sex-related differences in geno-type negative patients or patients who have not been genotyped. A rare form of SQTS often diagnosed as bradycardia in utero has a different sex distribution than other types of SQTS, with 8 out of 10 cases been diagnosed in females, but more cases are needed to make a firmer statement regarding this observation. As this review has clearly shown, we need more individual data on more patients in order to improve our knowledge about SQTS. The multicenter study by Mazzani et al. [39] is a step in the right direction but ought to include more centers as an International SQTS Registry.

Addendum

In most of the articles referred to in this chapter as well as in the chapter itself QT interval duration has been presented as the QT interval corrected by Bazett's formula. Given that the QTc interval by this formula is inversely related to the square root of heart rate, the QTc interval may be shorter simply as a result of a longer RR interval without necessitating any change in absolute value. When this possibility was examined by Lehmann et al. [52] in a large group of subjects from families with LQTS, it was concluded that a rate artifact alone could not account for the observed

age-sex differences in the QTc interval in this group of patients. There are at present not enough data from studies of patients with SQTS to perform a similar evaluation in this group of patients, but in the age group 20–50 years where the prevalence of males among patients with SQTS is much higher than the prevalence of females (Fig. 23.2), there is minimal difference in average heart rate between the two sexes (males 68 bpm, females 71 bpm). Despite the fact that Bazett's formula is particularly inaccurate in patients with SQTS due to the minimal change in QT interval with heart rate in these patients, it is therefore unlikely that a heart rate artifact alone can account for the observed age–sex differences in the QTc interval, just as in the case of patients with LQTS.

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Chapter 24

Sex differences in Brugada syndrome

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Introduction

In 1992, two Spanish cardiologist brothers, Pedro and Josep Brugada, reported eight patients with recurrent episodes of aborted sudden death and no demonstrable heart disease having a peculiar electrocardiographic (ECG) pattern of ST elevation in right precordial leads [1]. The Brugada syndrome (BrS), one of the most devastating causes of sudden cardiac death (SCD) in relatively young patients with apparently normal hearts, was born. In fact, it is likely that the first cases of BrS were reported a few years before in Italy [2] and in Japan [3,4]. Moreover, a mysterious syndrome of sudden unexpected nocturnal death (SUNDS) had been known for more than 1st century in Manila, Guam, and Hawaii [5,6] and other Southeastern Asian countries [7–9] (Japan, Thailand, Korea, Laos, and Cambodia) under various appellations as well as among Southeast Asian refugees in the United States [10]. Later studies suggested that SUNDS and BrS are phenotypically, genetically, and functionally the same disorder [8]. However, this issue remains controversial [11].

The mechanism of BrS is attributed to a "repolarization" or "depolarization" disorder or both [12]. Mutations that affect cardiac ion currents have been linked to the syndrome. So far, mutations have been found in ~21 different genes; however, strong evidence of link to the disease has been established only for the cardiac sodium channel gene *SCN5A* [13].

Although the mode of inheritance has been recently questioned [14] (inheritance of multiple BrS susceptibility variants [oligogenic] acting in concert through one or more mechanistic pathways rather than autosomal dominant mode of transmission of a single mutation [classic mendelian view)]), malignant BrS is surprisingly uncommon in females, representing less than 10% of the patient population with arrhythmic events (AEs) [15,16]. The largest series that included females with aborted cardiac arrest (ACA) comprised seven to nine females [17,18] and those with AEs on follow-up with or without an ICD included merely up to four females [19–22]. This explains the difficulty of accurately comparing the clinical, ECG, electrophysiologic, and genetic characteristics of males and females with BrS and AEs.

We recently reported the results of a multicenter international survey (SABRUS) on a large cohort of 678 BrS patients with their first ever documented AE, including 59 females [15,16,23]. In this large cohort, we observed several sex differences including novel findings [23]. In the present chapter, we will review the main sex differences in BrS patients in light of the SABRUS results.

The ECG pattern in Brugada syndrome

The Brugada ECG nomenclature has evolved over the years. In 2002, the proposed consensus paper on BrS recognized three types of repolarization patterns [24] (Fig. 24.1). Type 1 is characterized by a prominent coved ST-segment elevation and displays a J-wave amplitude or elevated ST-segment elevation $\geq$2 mm or 0.2 mV at its peak followed by a negative T wave, with little or no isoelectric separation. Type 2 also has a high take-off ST-segment elevation, but the J-wave amplitude ($\geq$2 mm) gives rise to a gradually descending ST-segment elevation (remaining $\geq$1 mm above the baseline) followed by a positive or biphasic T wave resulting in a saddle back configuration. Type 3 includes a right precordial ST-segment elevation comprising a $\leq$1 mm saddle back or coved configuration (or both). According to the recent consensus conference of J-wave syndromes in 2016 [14], only spontaneous type 1 Brugada–ECG pattern (BrEP) is the basis for the diagnosis of BrS. However, if the type 1 BrEP is unmasked by either fever or a drug challenge test, the patient needs to additionally have an appropriate clinical presentation, family history, or genetic analysis, as

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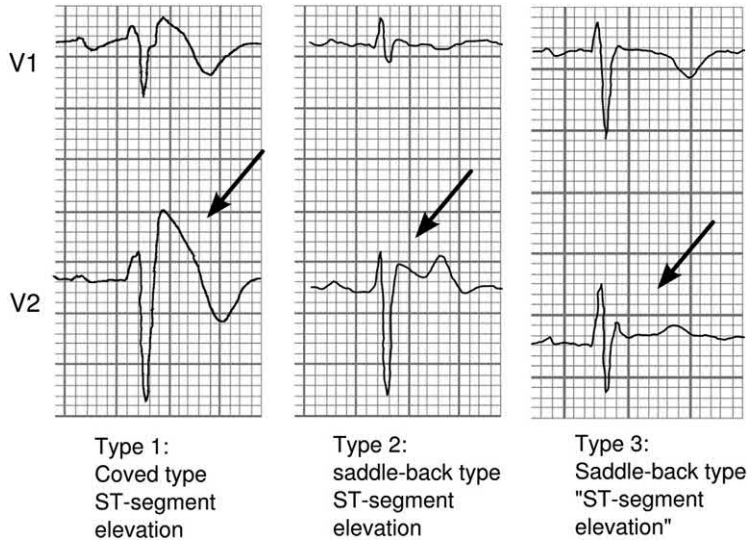

FIGURE 24.1 **The three types of Brugada ECG.** Reproduced from *Mizusawa Y, Wilde AA. Brugada syndrome. Circ Arrhythm Electrophysiol 2012;5:606–616.*

proposed by the Shanghai Scoring System, to achieve a score of >3.5 for the definite diagnosis of BrS [14]. Consequently, the prevalence of the BrEP in the literature has shifted according to year of publication and geographic region [25]. This is complicated even more by the fact that the BrEP prevalence is markedly dependent on sex and ethnicity [25,26].

The worldwide prevalence of Brugada–ECG patterns according to sex

The worldwide BrEP prevalence was assessed in two metaanalyses. Quan et al. [27] were the first to retrieve 24 studies dealing with the issue and found a mean worldwide prevalence of BrEP of 0.4%, with higher rates observed in males (0.9%) compared to females (0.1%). In addition, this difference was constant throughout all geographic regions, with highest figures detected in Asia (1.9% and 0.2% in males and females, respectively). However, Quan et al. [27] included all three subtypes of BrEP together in their analysis.

The second metaanalysis by Vutthikraivit et al. [26] separated spontaneous or drug-induced type 1 BrEP from types 2/3. The investigators congregated 369,068 patients from 28 published reports and calculated separate pooled prevalence of type 1 BrEP to be 0.05% (95% confidence interval [CI]: 0.03%–0.07%) while that of types 2/3 BrEP was 0.6% (95% CI: 0.5%–0.7%). Of the 28 studies, 17 reported on sex differences enabling the observation that type 1 BrEP (either spontaneous or drug-induced) and type 2/3 BrEP were 6 times and 2.8 times more common in males than in females, respectively.

The worldwide prevalence of spontaneous type 1 Brugada–ECG pattern according to sex

The prevalence of spontaneous type 1 BrEP recorded at the standard intercostal leads, assessed by Shi et al. [25] in their metaanalysis of a healthy worldwide population, was reported to be 0.03%. However, a substantial heterogeneity among studies was observed, and by metaregression analysis, region and year of publication, as well as sample size, were the main sources for the heterogeneity. Unfortunately, Shi et al. [25] did not separate the prevalence by sex and only stated that from the studies included, the incidence of BrEP was consistently higher in male participants than in females, with an odd ratio of 3.34 [25].

Table 24.1A summarizes the available literature on the world prevalence of spontaneous type 1 BrEP in the healthy male and female population. Out of 16 studies included (n = 88,415), 7 were from East Asian countries (4 from Japan and 1 from China, Taiwan, and Thailand each, n = 52,284). The proportion of males (51.5%) and females (48.5%) was similar. The prevalence of each BrEP type was calculated for both sexes, and the male-to-female ratio between Asian and non-Asian countries was compared for spontaneous type 1 BrEP alone (Table 24.1B). Spontaneous type 1 BrEP was significantly more frequently observed in males from Asian regions (0.32% vs. 0.036% in females, $P < .001$). In non-Asian patients, the prevalence of spontaneous type 1 BrEP was also higher in males but the difference did not reach statistical significance (0.11% vs. 0.05% in males and females, respectively, $P = .054$). The M/F ratio was much higher in patients from Asian countries (n = 8.9) compared to patients from non-Asian countries (n = 2.2).

TABLE 24.1A World prevalence of spontaneous type 1 BrEP in the healthy population according to published literature.

Author (Refs.)	Year	Geographic area	Total Pts	Total Pts (%)			Total Male	Male Pts (%)			Total Female	Female Pts (%)		
				Sp Type 1	Type 2/3	Total		Sp Type 1	Type 2/3	Total		Sp Type 1	Type 2/3	Total
Hermida et al. [76]	2000	France	1,000	1 (0.1)	60 (6)	61 (6.1)	630	1 (0.16)	60 (9.5)	61 (9.68)	370	0	0	0
Miyasaka et al. [77]	2001	Japan	13,929	17 (0.12)	81 (0.58)	98 (0.7)	3,691	14 (0.38)	65 (1.76)	79 (2.14)	10,238	3 (0.03)	16 (0.16)	19 (0.19)
Furuhashi et al. [78]	2001	Japan	8,612	4 (0.05)	8 (0.09)	12 (0.14)	5987	4 (0.07)	7 (0.12)	11 (0.18)	2,625	0	1 (0.04)	1 (0.04)
Bozkurt et al. [79]	2006	Turkey	1,238	1 (0.08)	5 (0.4)	6 (0.5)	671	1 (0.15)	4 (0.59)	5 (0.74)	567	0	1 (0.17)	1 (0.17)
Letsas et al. [80]	2007	Greece	11,488	2 (0.03)	23 (0.2)	25 (0.23)	6663	2 (0.03)	21 (0.31)	23 (0.34)	4,825	0	2 (0.04)	2 (0.04)
Bigi et al. [81]	2007	Iran	3895	14 (0.36)	86 (2.2)	100 (2.6)	1791	11 (0.61)	55 (3.07)	66 (3.7)	2,104	3 (0.14)	31 (1.47)	34 (1.61)
Liang et al. [82]	2007	China	1,001	0	47 (4.7)	47 (4.7)	877	0	47 (5.35)	47 (5.35)	124	0	0	0
Tsuji et al. [83]	2008	Japan	13904	37 (0.27)	61 (0.44)	98 (0.7)	3615	31 (0.86)	48 (1.32)	79 (2.18)	10,289	6 (0.06)	13 (0.13)	19 (0.18)
Gallagher et al. [84]	2008	Europe	12,012	2 (0.02)	29 (0.24)	31 (0.26)	10930	2 (0.02)	29 (0.26)	31 (0.28)	1,082	0	0	0
Wajed et al. [85]	2008	Pakistan	1100	2 (0.18)	7 (0.64)	9 (0.82)	712	1 (0.14)	6 (0.84)	7 (1)	388	1 (0.26)	1 (0.26)	2 (0.51)
Sinner et al. [86]	2009	Germany	4149	11 (0.26)	3 (0.07)	14 (0.34)	2034	9 (0.44)	3 (0.15)	12 (0.6)	2,115	2 (0.09)	0	2 (0.09)
Holst et al. [87]	2012	Denmark	340	0	43 (12.65)	43 (12.65)	278	0	37 (13.3)	37 (13.3)	62	0	6 (9.7)	6 (9.7)
Adler et al. [43]	2013	Israel	909	1 (0.11)	4 (0.44)	5 (0.55)	445	1 (0.22)	2 (0.45)	3 (0.67)	464	0	2 (0.43)	2 (0.43)
Juang et al. [88]	2015	Taiwan	5,214	4 (0.08)	169 (3.24)	173 (3.32)	2530	3 (0.12)	109 (4.3)	112 (4.42)	2,684	1 (0.04)	60 (2.3)	61 (2.3)
Tsuneoka et al. [89]	2016	Japan	7,178	8 (0.11)	84 (1.17)	92 (1.28)	2886	7 (0.24)	74 (2.56)	81 (2.8)	4,292	1 (0.02)	10 (0.23)	11 (0.26)
Rattanawong et al. [44]	2017	Thailand	2,446	10 (0.4)	21 (0.86)	31 (1.27)	1817	10 (0.55)	15 (0.82)	25 (1.37)	629	0	6 (0.95)	6 (0.95)

TABLE 24.1B Male-to-female ratio between Eastern Asian and non-Eastern Asian countries from the pooled prevalence of spontaneous type 1 BrEP.

	Male	Female	M/F
Eastern Asia	69 (0.32)	11 (0.036)	8.9
Non-Eastern Asia	28 (0.11)	6 (0.05)	2.2
Eastern Asia/Non-Eastern Asia	2.9	0.72	

Prevalence of spontaneous type 1 Brugada–ECG pattern in BrS patients with arrhythmic events

A higher prevalence of spontaneous type 1 BrEP has been observed in all studies of male BrS patients with AEs. Among 58 patients with AE, Sacher et al. [19] detected a spontaneous type 1 BrEP in 36 men (72%) but in only 2 women (25%) ($P = .02$). Sieira et al. [22] noticed a similar low prevalence (1 of 7 [14%]) of spontaneous type 1 BrEP in females with AEs. In contrast, in the PRogrammed Electrical stimUlation preDictive valuE registry [20], all three BrS females who exhibited an AE after a prophylactic ICD implantation had spontaneous type 1 BrEP. In the largest cohort of BrS patients with AEs (SABRUS) [23], a spontaneous type 1 BrEP was observed in 69% (427 out of 619) of males and 41% (24 out of 59) of females with AEs ($P < .001$) [23] (Fig. 24.2). Although these results confirm the lower female prevalence of spontaneous type 1 BrEP, the relatively high figure of 41% in females with AEs has never been reported previously.

Clinical outcome of patients with the type 1 Brugada ECG

As stated previously, most BrS patients presenting with spontaneous type 1 BrEP are males. Numerous studies have assessed the prognostic value of a type 1 BrEP (either spontaneous or drug induced), and most found it to be a risk factor when associated with syncope. In asymptomatic patients with type 1 BrEP, limited studies reported on a lower risk of SCD [21,28–34]. In a recent metaanalysis, Delise et al. [35] confirmed that the arrhythmic risk depends on whether the type 1 BrEP is spontaneous or drug-induced. In the former case, the annual incidence of SCD proved to be 0.9% per year, while it was 0.08% in the latter. An important observation was that most of the patients who exhibited an ACA were males in their 40s [35], emphasizing the important role of sex. The most recent data by Berthome et al. [36] on 494 females with BrS corroborated that spontaneous type 1 BrEP was less frequent in women (22% vs. 36% in males, $P < .001$), and contrary to men, it was not associated with cardiac events (HR: 2.5, 95% CI: 0.8 to 8, $P = .12$).

SABRUS assessed the incidence of spontaneous type 1 BrEP in BrS patients with AEs [23]. As specified earlier, in the whole study group, a spontaneous type 1 BrEP was recognized in 69% of males and 41% of females ($P < .001$); however, this difference disappeared above the age of 60, with a similar high incidence (≈65%) in both sexes [23] (Fig. 24.2). These results suggest that aging might contribute to the development of a type 1 BrEP, through age-related (ultra) structural abnormalities, as observed in *SCN5A*-knockout mice [37]. More intriguing is the association of spontaneous type 1 BrEP with an earlier onset of AEs in the pediatric group of females compared to males [23]. This observation advocates spontaneous type 1 BrEP to be a significant arrhythmic risk marker in pediatric females. Further analysis of our data [23] according to patient clinical presentation revealed that females in the ACA group presented significantly less with a spontaneous type 1 ECG compared to males (27% vs. 68% respectively, $P < .0001$, unpublished data). However, this sex difference was not

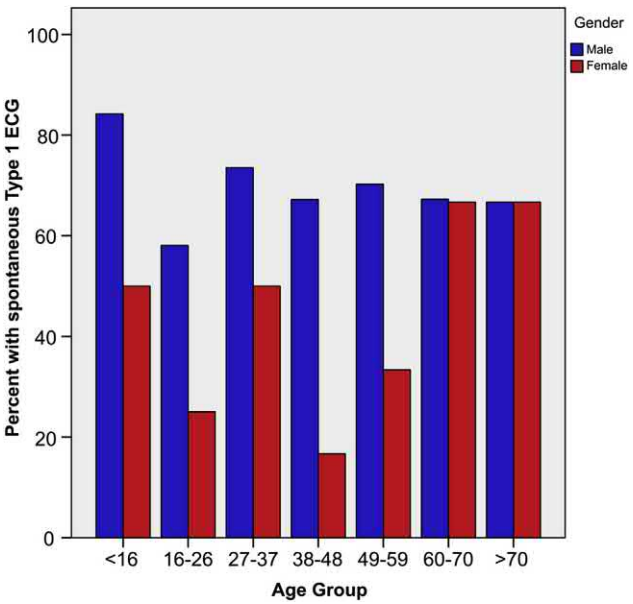

FIGURE 24.2 Prevalence of spontaneous type 1 BrEP in the SABRUS cohort. Reproduced from *Milman A, Gourraud JB, Andorin A, Postema PG, Sacher F, Mabo P, et al. Gender differences in patients with Brugada syndrome and arrhythmic events: data from a survey on arrhythmic events in 678 patients. Heart Rhythm 2018;15:1457–65.*

present in the group of patients who exhibited their AE after a prophylactic ICD implantation (60% in females vs. 70% in males, $P = .35$, unpublished data). These findings stress the difficulty of risk stratification in female BrS patients.

Arrhythmic events in Brugada syndrome

AEs are surprisingly uncommon in females compared to males. Sieira et al. [22] reported on the highest female AE rate (6 of 23%, 26%) in a series of 542 BrS patients (42% females). They explained their large female cohort by a proactive search of BrS and an exhaustive familial screening program performed at their institution. SABRUS collected the largest cohort of BrS patients with AEs (n = 678) and confirmed the actual low involvement of AEs in females (8.7%, 59 females of the 678 SABRUS population), especially in those of Asian ethnicity [23] (Fig. 24.3).

Age at onset of arrhythmic events

The vast majority of BrS patients exhibit their first AE between 20 and 65 years of age with a mean age at time of AE ranging from 39 to 48 years [15,17,18,33]. Fig. 24.4 illustrates the age distribution of AE in 678 SABRUS patients. Previous studies have consistently shown that females were older than males at time of AE; nonetheless, the difference never reached statistical significance probably due to the low number of female patients included in these studies [17,19]. In SABRUS, the difference of 6.5 years between the mean ages of adult females and males (>16 years old) at time of AE was very significant ($P = .001$) possibly attributable to the inclusion of a large female cohort [15] (Fig. 24.5). Interestingly, in the pediatric SABRUS group, there was no sex difference between the ages at time of AE. Furthermore, Berthome et al. [36] observed a similar difference in the mean age at BrS diagnosis of 47 ± 16 years in women versus 44 ± 14 years in men ($P = .002$) [36].

Mode of clinical presentation

Table 24.2 summarizes the published series of BrS patients with sex distribution according to the mode of arrhythmic presentation. A total of 2726 patients (77.3% males) were collected in 10 series. Male predominance was the highest in patients who presented with ACA (92.6%), intermediate in those who presented with syncope (76.2%), and the lowest in the asymptomatic patients (71%). The male/female ratios in these three groups of patients were 12.5, 3.2, and 2.5, respectively. In SABRUS, the M/F ratio in patients with AE for all 678 patients was 10.1. Fig. 24.6 illustrates how the M/F ratio was dependent on the patient age group, being the highest (25.2) in the 27–37 years age group and the lowest (1.9–2.0) in the pediatric and elderly patient groups.

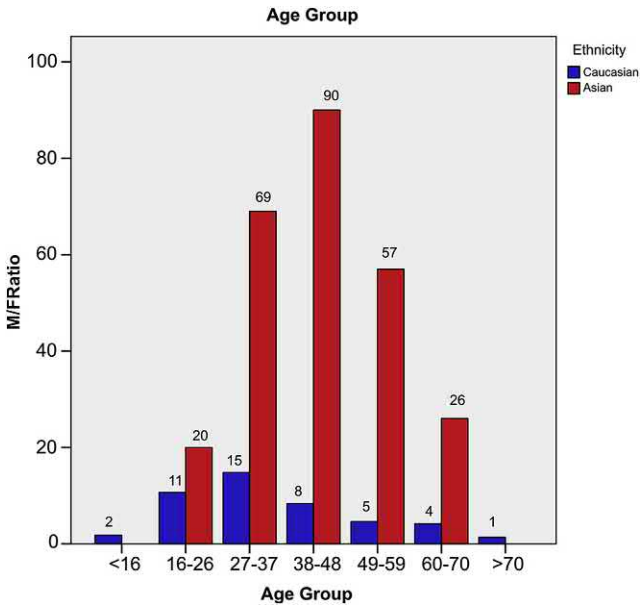

FIGURE 24.3 Male-to-female (M/F) ratio of arrhythmic event (AE) by ethnicity in various age groups in the 678 SABRUS patients. In the SABRUS, the M/F ratios were markedly greater in Asians than in Caucasians. The greatest M/F ratios were observed for Asians in the 38- to 48-year-old age group in SABRUS (n = 90). Reproduced from *Milman A, Gourraud JB, Andorin A, Postema PG, Sacher F, Mabo P, et al. Gender differences in patients with Brugada syndrome and arrhythmic events:data from a survey on arrhythmic events in 678 patients. Heart Rhythm 2018;15:1457–65.*

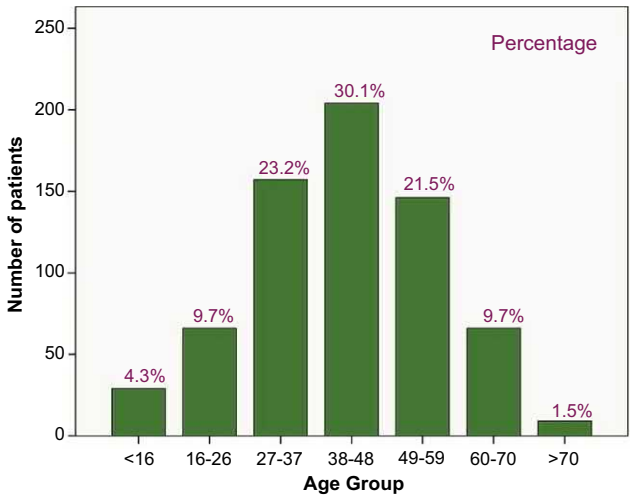

FIGURE 24.4 Age distribution of AE in the 678 SABRUS patients. The age of first AE is normally distributed with a single peak in the 38–48 years age group. Reproduced from *Milman A, Andorin A, Gourraud JB, Sacher F, Mabo P, Kim SH, et al. Age of first arrhythmic event in Brugada syndrome: Data from the SABRUS (Survey on Arrhythmic Events in Brugada Syndrome) in 678 patients. Circ Arrhythm Electrophysiol 2017;10. pii: e005222. doi: 10.1161/CIRCEP.117.005222. Epub December 18, 2017.*

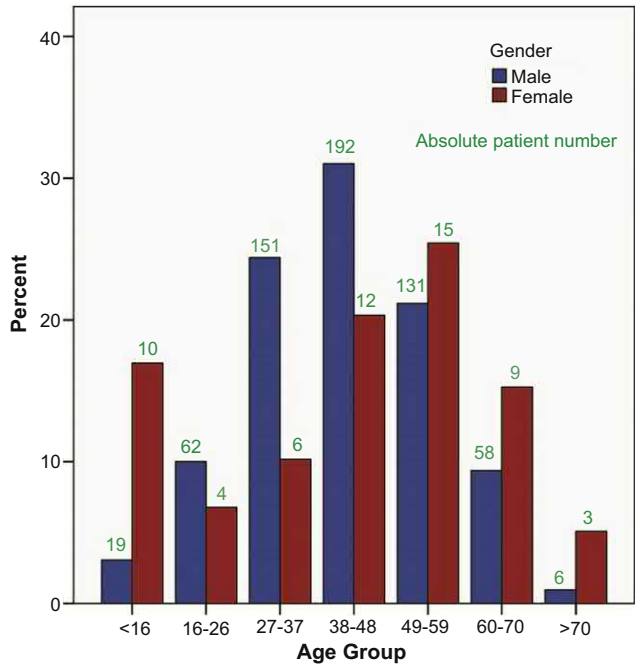

FIGURE 24.5 **Age distribution by sex in SABRUS.** Age is normally distributed in males, while the female distribution is abnormal due to a high prevalence of AE in females of prepubescent age. Females exhibit their AE at a significantly older age than males. Reproduced from *Milman A, Andorin A, Gourraud JB, Sacher F, Mabo P, Kim SH, et al. Age of first arrhythmic event in Brugada syndrome: Data from the SABRUS (Survey on Arrhythmic Events in Brugada Syndrome) in 678 patients. Circ Arrhythm Electrophysiol 2017;10. pii: e005222. doi: 10.1161/CIRCEP.117.005222. Epub Dec 18, 2017.*

Fever-related arrhythmic events

Several factors are known to precipitate an AE in BrS patients such as specific drugs [38], increase in vagal tone [39], and fever [40]. Dumaine et al. [41] were the first to link temperature with the function of a mutant *SCN5A* sodium channel. Later, it was demonstrated that fever may induce type 1 BrEP in BrS patients [42]. Two large studies showed that in unselected populations with fever, type 1 BrEP may be seen in 2%–4% of patients [43,44], but none of these patients experienced malignant AEs. However, Mizusawa and colleagues [45] subsequently proved that, as opposed to patients who have only drug-induced type 1 ECG, those with fever-induced type 1 ECG are at increased risk for syncope and VF.

Michowitz et al. [46] reported that ≈ 6% of AEs in SABRUS were associated with fever. These AEs occurred mainly in Caucasian males, at all age groups and often presented as ACA. The highest proportion of fever-related AEs was observed in the pediatric population (age <16), with disproportionally higher event rates in the very young (0–5 years old). Marked sex differences were noted; with males included in all age groups contrasting with an exclusive female involvement in the pediatric and elderly groups (Fig. 24.7).

Electrophysiologic studies

Historical notes

The prognostic value of electrophysiologic study (EPS) in BrS remains a controversial issue, especially in females. Going back to 2001, Pedro Brugada et al. reported that the inducibility of a sustained ventricular arrhythmia was a good predictor of outcome in BrS and that asymptomatic patients can be reassured if they are noninducible [47]. In 2002, Josep Brugada et al. were the first to propose, on the basis of data from their registry, that sustained ventricular arrhythmia inducibility at programmed electrical stimulation (PES) is useful in identifying patients at high risk of sudden death [48]. However, at the same time, Priori et al. were unable to confirm the predictive value of PES in their BrS cohort and suggested that the use of the test might result in unnecessary insertion of an ICD due to low test specificity [49]. Of note, both studies [48,49] comprised a minority of females ranging from 23.6% [48] to 15.4% [49] and did not address possible sex-related differences in PES results.

Since then, many studies focused on this issue [17,18,32,50]; however, the only prospective study specifically designed to examine the prognostic yield of EPS in BrS was the PRELUDE registry, which concluded that, regardless the protocol used, the induction of ventricular arrhythmias with PES is not useful for identifying high-risk patients with BrS [20]. Of note, 14 patients from the PRELUDE registry suffered an AE during follow-up; 3 of them were female patients and only 1 of the 3 had a positive EPS [20].

Recently, Sroubek et al. [51], addressed the value of EPS for risk stratification in a multicenter pooled analysis of 1312 BrS patients (79% males) without prior cardiac arrest who underwent PES in 8 centers. Noteworthy is that Priori's group but not the Brugada brothers participated in this analysis. Induction of sustained ventricular tachyarrhythmias with PES was associated with a two- to threefold increased risk of AEs over a median follow-up of 38 months. The risk was greatest among individuals who had their arrhythmias induced with a single or double extrastimuli. Individuals who had no inducible arrhythmias exhibited a low AE risk (≈1% per year), though the risk varied substantially according to associated clinical features such as a history of syncope and the presence of a spontaneous type 1 BrEP. Collectively, these findings indicate that clinical features effectively stratify individuals at highest and lowest arrhythmic risk and that PES with single or double extrastimuli may be most useful for predicting arrhythmia in intermediate risk individuals [51]. However, the lack of induction does not necessarily portend low ventricular arrhythmia risk, particularly in patients with high-risk clinical features. It is noteworthy that their study did not assess whether sex could influence the results.

TABLE 24.2 The published series of BrS-patients with gender differences according to the mode of presentation.

Author (Refs.)	Year	Geographic area	Total Pts	Aborted cardiac arrest		p value	Syncope		p value	Asymptomatic		p value
			M/F	Total Male	Total Female		Total Male	Total Female		Total Male	Total Female	
Atarashi et al. [90]	2001	Japan	99/6	20	0		17	1		62	5	
Masaki et al. [91]	2002	Japan	12/1	1	0		2	0		9	1	
Mok et al. [92]	2005	Hong Kong	47/3	8	0		12	0		27	3	
Furushima et al. [93]	2005	Japan	23/1	7	0		8	0		8	1	
Kharazi et al. [94]	2007	Iran	11/1	3	0		7	0		1	1	
Ohkubo et al. [95]	2007	Japan	33/1	2	0		9	0		22	1	
Probst et al. [17]	2010	Europe	745/284	55	7		238	75		452	202	
Son et al. [34]	2013	Korea	68/1	37	1		17	0		14	0	
Makarawate et al. [96]	2014	Thailand	88/2	64	1		13	1		11	0	
Sieira et al. [22]	2016	Europe	314/228	17	6		82	51		215	171	
Calo et al. [97]	2016	Italy	272/75	28	4		27	12		217	59	
Hernandez-Ojeda et al. [98]	2017	Europe	91/13	10	0		41	8		40	5	
Holst et al. (*)	2018	Denmark	25/6	9	1		7	3		9	2	
Rivard et al. (*)	2018	Canada	85/22	7	3		34	5		44	14	
Total			1828/622	261 (14.3%)	20 (3.2%)	<0.0001	480 (26.2%)	151 (24.3%)	0.33	1087 (59.5%)	451 (72.5%)	<0.001

**personal communication*

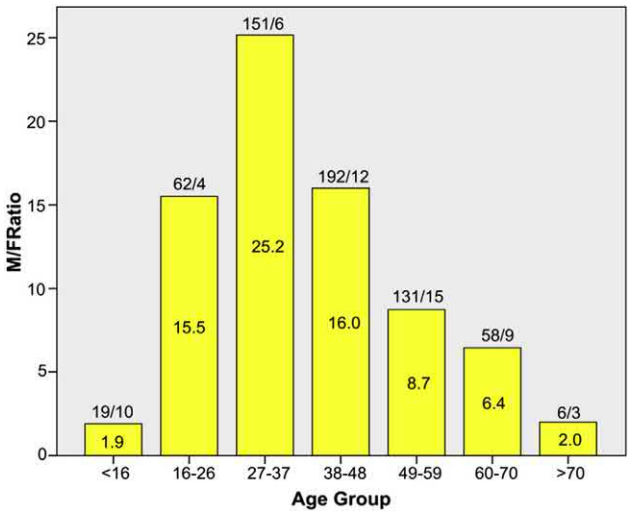

FIGURE 24.6 Male-to-female (M/F) ratio of arrhythmic event (AE) in various age groups in the 678 SABRUS patients. The M/F ratio is indicated into the bars for each age group. The numbers above the bars indicate the absolute numbers of males and females, respectively, for each age group. In SABRUS, the M/F ratios were the highest in the 27–37 years age group. Reproduced from *Milman A, Gourraud JB, Andorin A, Postema PG, Sacher F, Mabo P, et al. Gender differences in patients with Brugada syndrome and arrhythmic events: data from a survey on arrhythmic events in 678 patients. Heart Rhythm 2018;15:1457–65.*

Electrophysiologic studies in females with BrS

Benito et al. were the first to report on a lower inducibility rate of sustained ventricular tachyarrhythmias in BrS females (12% vs. 32% in males, $P < .01$) [21]. Their study population constituted of 112 females, most (85%) asymptomatic, including only 1 female with a history of SCD. Upon follow-up, 3 women (counting two who were asymptomatic at baseline) suffered an AE; one of these two asymptomatic females underwent an EPS and had an inducible ventricular arrhythmia. As opposed to females, males with AEs on follow-up had significantly higher inducible arrhythmias than those who remained asymptomatic (74% vs. 28% respectively, $P < .001$) [21]. These findings emphasize the problematic risk stratification of females by means of EPS.

Sacher et al. [19] obtained dissimilar results. They studied 8 females (all with AEs) and compared them to 50 symptomatic males. They could not find a significant difference in arrhythmia inducibility rate between females (50%) and males (76%). Remarkably, their study population included only severely symptomatic patients, as opposed to the study by Benito et al. [21], which included mostly asymptomatic patients. Interestingly, when analyzing only the symptomatic patients from the Benito et al. group [21], the inducibility rates (50% for females and 74% for males) were similar to the respective observations found by Sacher et al. [19]. These figures should be taken with caution because of the limited sample of females who underwent an EPS (n = 4 [19] and n = 2 [21]).

Nevertheless, the latest report by Sieira et al. shed new light on the subject [22], when 228 females were compared to 314 males. Once again, a lower inducibility rate during EPS in females (5.5% vs. 22.3% in males, $P < .01$) was observed in the overall BrS cohort. After classifying females according to their primary clinical presentation, the authors stated that females with inducible arrhythmias presented frequently more with symptoms (ACA and syncope in 63.6% and 24.7% of patients, respectively);

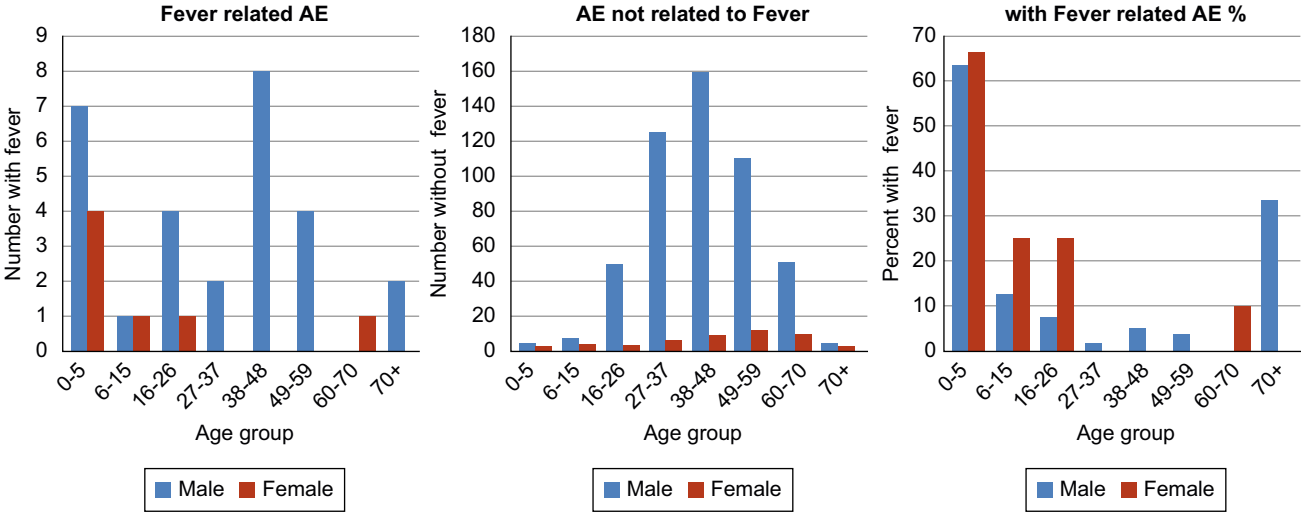

FIGURE 24.7 Age distribution in males and females with (left panel) or without (middle panel) fever-related AE. The percentage of patients in each sex with fever-related AE in each age group is presented on the right panel. Since the only females in age groups 16–26 and 60–70 were 16 and 70 years old, respectively, there are no cases of females with fever-related AE between ages 17–69. Reproduced from *Michowitz Y, Milman A, Sarquella-Brugada G, Andorin A, Champagne J, Postema PG et al. Fever-related arrhythmic events in the multicenter Survey on Arrhythmic Events in Brugada Syndrome. Heart Rhythm 2018;15:1394–401.*

however, on follow-up, out of their 7 women with AEs, EPS were performed in only 5 and solely one was inducible. Notably, there were two asymptomatic females in this group, one with a negative EPS and the other who refused the test [22]. Overall, Sieira et al. [22] concluded that arrhythmia inducibility does not predict a higher risk of AEs and, more importantly, stressed the worrisome observation that a negative EPS might not lead to a lower risk category in females. Lastly, Berthome et al. [36] compared the EP results in both sexes of BrS patients and various clinical presentations. They observed inducible ventricular tachyarrhythmias in 27% and 42% of women and men, respectively ($P = .003$).

In the SABRUS population which exclusively included patients with AEs and comprised a large female cohort (n = 59), the lower arrhythmia inducibility rate of BrS females was confirmed (36% vs. 66% in males, $P < .001$) [23] (Fig. 24.8). Additional analysis of the SABRUS results according to patient presentation prior to documented AE allowed further interesting observations [23]. The arrhythmia inducibility rates were significantly lower in females presenting with ACA (25% vs. 58% in males, $P = .005$) and in those presenting with syncope (40% vs. 73% in males, $P = .009$). In contrast, similar high inducibility rates were found in both asymptomatic sexes (75% and 76%, respectively, P=NS). These results should encourage performing an EPS in asymptomatic patients regardless their sex; however, the relatively low number of females included in this patient group precludes definite conclusion.

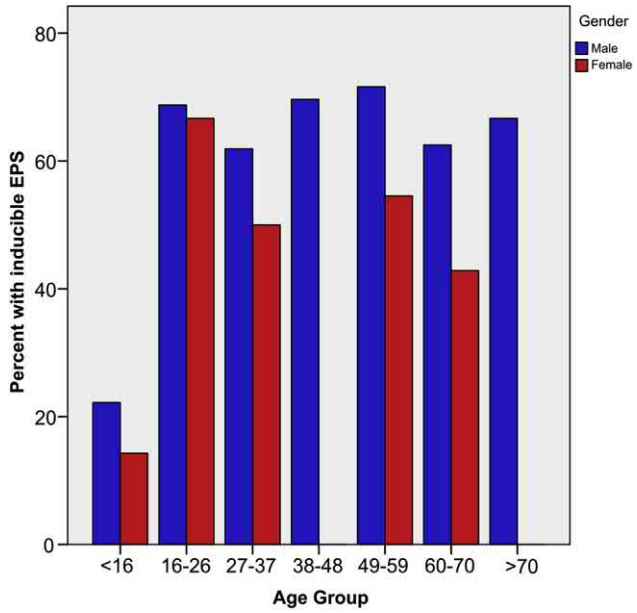

FIGURE 24.8 Sex comparison of the proportions of patients with inducibility of ventricular fibrillation at electrophysiologic study in the SABRUS. Reproduced from *Milman A, Gourraud JB, Andorin A, Postema PG, Sacher F, Mabo P, et al. Gender differences in patients with Brugada syndrome and arrhythmic events:data from a survey on arrhythmic events in 678 patients. Heart Rhythm 2018;15:1457–65.*

Genetics

Of 21 suggested genes to cause BrS, an expert panel classified only *SCN5A* as having definitive evidence [13]. Because all mutations thus far identified in *SCN5A* display an autosomal dominant mode of transmission, males and females would be expected to inherit the defective gene equally [52]; however, BrEP phenotype is 8–10 times more prevalent in men than in women [53,54]. In the past decades, more observations suggest that BrS has a heterogeneous genetic basis and is a disease with a more complex inheritance [55].

The prevalence of *SCN5A* mutation

Approximately 30%–35% of clinical BrS cases can be genetically classified, indicating that 65%–70% remain genetically unresolved [55,56]. Prior studies have not established a different prevalence in mutation carriers according to sex [19]; however, the incidence of *SCN5A* mutation has been found to markedly vary according to patients' ethnicity [55]. The latter observation was hypothesized to result from diverse distribution of disease-causing genes among BrS patients from Asia compared to the Caucasian population. Furthermore, certain *SCN5A* promoter polymorphisms in a haplotype variant with a relatively high prevalence in Asians were reported to not only reduce transcriptional activity in vitro but also modulate variability in cardiac conduction as assessed by PR and QRS durations [57]. Berthome et al. [36] recently found significantly higher *SCN5A* mutation rates in asymptomatic females (26% vs. 20% in asymptomatic males, $P = .02$). We found similar results in four main centers participating in SABRUS but only for patients aged>16 years (mutation rates of 25.9% and 20.1% in females and males, respectively, $P = .0085$) (Table 24.3) [23]. It is noteworthy that in patients with AEs included in SABRUS, females showed a much higher *SCN5A* mutation rate than males (47.6% and 27.8%, respectively, $P = .007$) [23] (Fig. 24.9 and 24.10).

Clinical manifestation of the genotype

Sex differences in BrS have not been associated with variant distribution of specific gene mutations (most commonly *SCN5A*). The role of exact mutations seems to be of minor influence. On the one hand, patients with and without identified *SCN5A* mutations display a similar male predominance [58–60]; on the other hand, the same single mutation has been described for both a family with a male predominance and another with female phenotypic predominance [8,61]. However, in families with a particular

TABLE 24.3 Comparison of SCN5A mutation rates in SABRUS and a Registry of Asymptomatic BrS Subjects in respect to gender.

		Males	Females	P
	< 16 yrs	26/91 (28.6%)	34/110 (30.9%)	0.71
Registry	≥ 16 yrs	206/1025 (20.1%)	137/528 (25.9%)	0.0085
	All ages	232/1116 (20.8%)	171/638 (26.8%)	0.004
	< 16 yrs	10/15 (66.7%)	7/10 (70%)	0.86
SABRUS	≥ 16 yrs	113/428 (26.4%)	13/32 (40.6%)	0.082
	All ages	123/443 (27.8%)	20/42 (47.6%)	0.007

The Registry data originated from the following four SABRUS centers:
- L'Institut du Thorax, Service de Cardiologie, CHU de Nantes, Nantes, France (n=1104 subjects);
- Division of Cardiology, University of Torino, Torino, Italy (n=288 subjects);
- Heart Rhythm Management Centre, UZ-VUB, Brussels, Belgium (n=205 subjects);
- Pediatric Arrhythmias, Electrophysiology and Sudden Death Unit Cardiology Department, Hospital Sant Joan de Déu, Barcelona, Spain (n=157 subjects).
Reproduced from Milman A, Gourraud JB, Andorin A, Postema PG, Sacher F, Mabo P, et al. Gender differences in patients with Brugada syndrome and arrhythmic events: data from a survey on arrhythmic events in 678 patients. Heart Rhythm 2018;15:1457–65.

SCN5A mutation, Kyndt et al. [62] reported a BrS phenotype in males but an isolated cardiac conduction defect in females.

In almost all published series, *SCN5A* gene characteristics did not influence AE rate. However, some studies identified a significantly higher rate of syncope among patients carrying *SCN5A* truncation and missense mutations resulting in a nonfunctional Na^+ channels, compared to *SCN5A* missense mutations that formed a reduced Na^+ current [63]. The discovery of common polymorphisms located at the same gene that can modulate the deleterious effects of mutations causing BrS [64,65] and improve the BrS phenotype offers a possible target for therapeutic interventions.

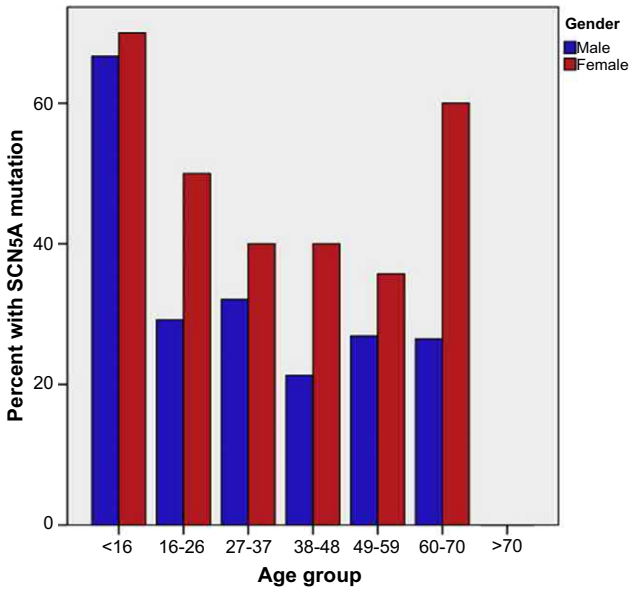

FIGURE 24.9 SCN5A mutations rates in SABRUS according to sex in respect to patient age group at the time of AE occurrence. Higher mutation rates were observed in females at all age groups with the highest figures (70% and 60%) observed in the pediatric and the 60–70 years age group, respectively. Of note the highest mutation rate in males (66.7%) was also found in the pediatric group. Reproduced from *Milman A, Gourraud JB, Andorin A, Postema PG, Sacher F, Mabo P, et al. Gender differences in patients with Brugada syndrome and arrhythmic events:data from a survey on arrhythmic events in 678 patients. Heart Rhythm 2018;15:1457–65.*

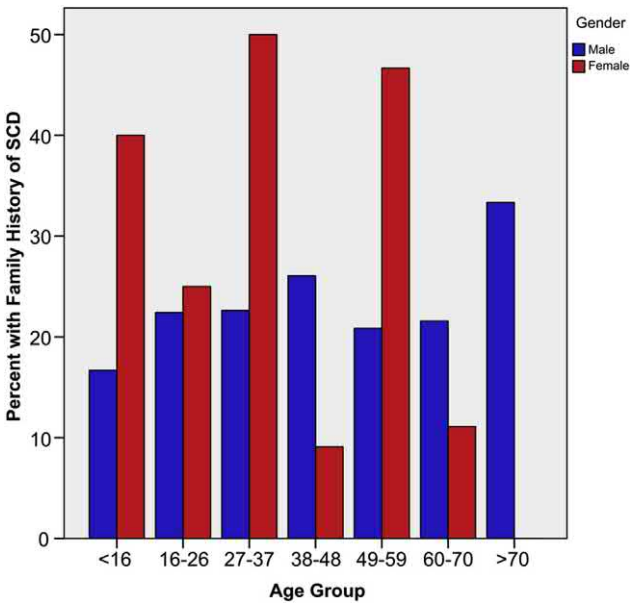

FIGURE 24.10 Sex comparison of the proportions of patients with a family history of sudden cardiac death in SABRUS. Reproduced from *Milman A, Gourraud JB, Andorin A, Postema PG, Sacher F, Mabo P, et al. Gender differences in patients with Brugada syndrome and arrhythmic events:data from a survey on arrhythmic events in 678 patients. Heart Rhythm 2018;15:1457–65.*

Clinical outcome of patients with the *SCN5A* mutation

Data outlining the possible use of genetics for risk stratification are scarce. The PRELUDE [20] and FINGER [17] studies in accordance with previous published results [28,59] concluded that BrS patients who carry a pathogenic variant of *SCN5A* display pronounced cardiac conduction defects not found in noncarriers. Moreover, patients with a truncated protein exhibited greater conduction disorders without an increased risk of SCD [63]. In contrast, a metaanalysis of the main BrS genetic databases available reported no different risk of life-threatening arrhythmias in carriers of a pathogenic variant in the *SCN5A* gene [30]. Taking all data into account, to date, genetic analysis has not been helpful in determining clinical risk.

Opposed to the abovementioned findings, a recent Japanese study involving 97% of males presented *SCN5A* mutation as a significant predictor of cardiac events in BrS *probands* [66]. Interestingly, Milman et al. [23] observed the *SCN5A* mutation rate to be slightly higher in the male SABRUS patients compared to a large cohort of asymptomatic male BrS patients (27.8% vs. 20.8%, $P < .001$). However, the same comparison in females yielded substantially higher differences (47.6% vs. 26.8%, respectively $P < .001$). Therefore, the higher mutation rates observed in the female cohort with AEs could suggest that the presence of an *SCN5A* mutation might represent an important risk marker for AE in females and less so in males.

Moreover, when separating the SABRUS patients who underwent genetic testing according to their clinical presentation, a noticeable sex difference is found in the ACA group with 52.2% of females versus 23.8% of males being *SCN5A* mutation carriers ($P = .003$, unpublished data). However, in the syncope or asymptomatic groups, little difference in mutation carriers was observed between sexes. The overall *SCN5A* mutation prevalence in the entire SABRUS cohort was highest among the asymptomatic group (44.3%), followed by the syncope group (31.8%), and lowest in the ACA group (25.9%) (unpublished data). These findings support the usefulness of genetic testing for risk stratification, specifically in asymptomatic patients and even more so in females.

Electrophysiological mechanism of sex differences

Several explanations have been suggested as the electrophysiologic mechanism underlying the male predominance of spontaneous type 1 BrEP and AE. The penetrance of BrS is age- and sex-dependent, and most lethal events occur in men after the fourth decade of life [7,15,21]. This sex distinction is attributed to the presence of a more prominent I_{to} current giving rise to a more prominent notch in the action potential of right ventricular epicardial cells in males versus females [53]. Hormonal contribution has been suggested to play an important role in the development of BrEP and the promotion of AEs through testosterone that significantly increases expression of I_{to} currents [53,70,71]. Also, steroid hormone−responsive elements, particularly sensitive to testosterone, in genes involved in BrS such as *SCN5A* (which encodes the cardiac sodium channel) and *CACNA1C* (which encodes the L-type calcium channel) have been identified [72]. The fact that testosterone levels peak during the teen and early adult male years together with the incidence of BrEP [73], and that both sexes have a similar prevalence in childhood [74], may suggest that sex hormones contribute to the age dependent differences observed in BrS.

Estrogen was also attributed regulatory properties on the expression of I_{to} channels by diminishing the transcription of Kv4.3 demonstrated by Song et al. [75]. Based on this finding, Milman et al. [15,23] hypothesized that the low estrogen activity in prepubertal and postmenopausal females could play a role in the expression of I_{to} channels, thus decreasing the propensity for arrhythmias in this population. This assumption could explain the observation that females aged >16 years exhibited their AE >6 years later than males [15]. In addition, the finding by Michowitz et al. [46] of exclusive occurrence of fever-related AEs in young and elderly females while occurring at all age groups in males asserts the "arrhythmic protection" theory of females during their reproductive years. Consequently, one may speculate that the presence of estrogen, and not the absence of testosterone, protects from AEs in procreative females.

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Part VII

Drug-induced electrophysiology abnormalities

Chapter 25

Mechanisms of drug-induced QT interval prolongation

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Introduction

The association of drug intake with QT interval prolongation leading to potentially fatal cardiac arrhythmias was first recognized in 1964, when reports of quinidine-induced syncope due to polymorphic ventricular tachycardia were published [1,2]. Francois Dessertenne, in 1966, identified *torsade de pointes* (TdP) as a specific form of polymorphic ventricular tachycardia [3] that is invariably preceded by QT interval prolongation. Since then, several studies have shown that ventricular tachyarrhythmias like TdP leading to syncope or sudden cardiac death (SCD) are linked to drug-induced QT prolongation with QT interval values often exceeding 500 milliseconds (ms) [4]. In the last three decades, several cardiac and noncardiac drugs were found to cause QT prolongation and carry a high proarrhythmic risk and were withdrawn due to unacceptably high risk of ventricular arrhythmias and SCD [3,4]. This led to an increased regulatory focus toward evaluating the cardiac safety profile of new drugs. Since 2005, all new drugs with systemic effects are subjected to stringent tests for assessing proarrhythmic risk before receiving regulatory approval.

While drug-induced QT prolongation has been considered as a de facto surrogate biomarker for assessing the proarrhythmic risk of a drug, the risk of SCD and TdP due to drug-induced QT prolongation is also determined by several other factors such as age, concomitantly used medications and associated clinical conditions such as bradycardia, hypokalemia, hypomagnesaemia, ventricular hypertrophy, renal failure, central nervous system disorders, and heart disease as well as the baseline QT/QTc interval [5]. Female sex has also been identified as an important predisposing factor for drug-induced arrhythmias and sudden death [5–7]. In 1920, Bazett showed that the QT interval in women was longer than that in men by 24 ms [8]. It is now well-recognized that premenopausal women have a QTc interval that is 10–20 ms longer than that in men [9–11]. The clinical significance of this observation became apparent on analysis of databases and registries for drug-induced QT prolongation that revealed that women accounted for 70% of reported cases of TdP [12,13].

In this chapter, we review the current understanding of mechanisms of drug-induced QT prolongation, including its incidence, electrophysiological aspects, contribution of anatomic, autonomic, and hormonal factors to drug-induced QT prolongation, and differences in men and women. We also briefly review how better understanding of repolarization-related proarrhythmic risk has evolved in designing preclinical and clinical studies for assessing the risk of drug-induced QT prolongation of new drugs.

Incidence of drug-induced QT prolongation

The overall incidence of drug-induced QT prolongation in the general population is difficult to estimate because it is often transient and an ECG may not be recorded at the time when the QT interval is prolonged. Additionally, the International Classification of Diseases (10th revision) has no separate code for drug-induced QT prolongation. Drug-induced QT prolongation and TdP are reported under codes for ventricular tachycardia (VT), ventricular fibrillation (VF), or SCD resulting in underreporting of drug-induced cardiac arrhythmias as a distinct entity [14]. Molokhia et al. estimate that 5%–7% of all reports of VT, VF, or SCD are, in fact, cases of drug-induced QT prolongation [15].

The annual incidence of drug-induced TdP based on self-reporting in pharmacovigilance databases in Sweden,

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Germany, and Italy range from 0.8 to 1.2 per million person years [13,15,16]. A study from Berlin reviewed patient records for TdP, SCD, or syncope and found the incidence of TdP to be 3.2 per million person years, with 60% being drug-induced [16]. Drugs commonly associated with TdP from the adverse drug reactions reported to the WHO are listed in Table 25.1 [13]. These numbers are believed to be gross underestimates and drug-induced QT prolongation is much more common in clinical practice [13].

The incidence is even higher in hospitalized patients. In emergency department and intensive care unit populations, drug-induced QT prolongation may occur in 24%–35% of patients because of high prevalence of heart disease, paralytic stroke, electrolyte disturbances, altered drug pharmacokinetics due to renal and hepatic disorders, and concomitant use of multiple drugs that prolong the QT interval [17–19].

Drug-induced QT prolongation and TdP are also important from a regulatory perspective. De Ponti estimates that 60% of new molecular entities being developed as potential therapeutic agents are abandoned during drug development for their QT prolonging effect [20]. QT prolongation also accounts for around 26% of licensed drugs that were withdrawn from the market between 1990 and 2005 [21].

Electrophysiological aspects of drug-induced QT prolongation

Cardiac action potential: its phases and ion channels involved

The QT interval represents the duration of the ventricular cardiac action potential on the surface electrocardiogram with its shape and duration being the vectorial sum of the different electrical currents from all the individual cardiomyocytes that contribute to the compound ventricular action potential. The generation of the ventricular action

TABLE 25.1 The 20 drugs most commonly reported to be associated with *torsade de pointes* (TdP) based on ADR reports to WHO between 1983 and 1999.

Drug name	TdP (n)	Fatal (n)	Total (n)	TdP/total (%)
Sotalol	130	1	2,758	4.71
Cisapride	97	6	6,489	1.49
Amiodarone	47	1	13,275	0.34
Erythromycin	44	2	24,776	0.18
Ibutilide	43	1	173	24.86
Terfenadine	41	1	10,047	0.41
Quinidine	33	2	7,353	0.45
Clarithromycin	33	0	17,448	0.19
Haloperidol	21	6	15,431	0.14
Fluoxetine	20	1	70,929	0.03
Digoxin	19	0	18,925	0.10
Procainamide	19	0	5,867	0.32
Terodiline	19	0	2,248	0.85
Fluconazole	17	0	5,613	0.30
Disopyramide	16	1	3,378	0.47
Bepridil	15	0	384	3.91
Furosemide	15	0	15,119	0.10
Thioridazine	12	0	6,565	0.18
Flecainide	11	2	3,747	0.29
Loratadine	11	1	5,452	0.20

Fatal (n), number of ADR reports named TdP with fatal outcome; *TdP (n),* total number of ADR reports named TdP for this drug; *Total (n),* total number of ADR reports for this drug.
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potential is dependent on voltage-gated conductance through various cardiac ion channels that determine the balance between inward and outward ionic currents (Table 25.2). This cardiac action potential has five phases: fast upstroke (phase 0) followed by a spike (phase 1) and plateau morphology (phase 2) and further repolarization (phase 3), followed by the transmembrane voltage returning to the resting membrane potential (phase 4) [20,22].

Phase 0 is the rapid depolarization phase that occurs due to rapid influx of Na^+ ions (Fig. 25.1) into the cardiac cell due to opening of the Nav1.5 channels carrying the I_{Na} (rapid inward sodium) current. Phase 1 represents the onset of cardiac repolarization and is characterized by initial rapid repolarization that occurs due to outward movement of K^+ and Cl^- ions along with inactivation of the Nav1.5 channels. The outward flow of potassium ions occurs via the Kv(I_{to}) potassium channels resulting in the I_{to} (fast transient outward) current with the $I_{Cl(Ca)}$ or $I_{to(2)}$ (slow transient outward) current also contributing by transient outflow of calcium-activated chloride ions. Phase 2 represents the plateau phase of the cardiac action potential, which is sustained by a balance between inward $I_{Ca(L)}$ and I_{NCX} currents mediated by Cav1.2 (L-type calcium) channel and the Na^+–Ca^{++} (sodium–calcium) exchanger, respectively, and outward I_{Ks} (slow delayed rectifier potassium) current mediated by Kv channels. Phase 3 represents the stage of cardiac action potential where Cav1.2 channels close, while the Kv channels are still open, resulting in a net outward current that opens the $K_v11.1$ channel carrying the outward I_{Kr} (rapid delayed rectifier potassium) current and the $K_{ir}2.1$, $K_{ir}2.2$, and $K_{ir}2.3$ channels carrying the inward I_{K1} (rectifier potassium) current. This results in a rapid efflux of K^+ ions through these channels causing further repolarization. Phase 4 represents the phase when the resting membrane potential is at −80 and −64 mV, which is set by the I_{K1} current with contribution from the I_{KATP} (weak inward rectifier) current carried by ATP-dependent potassium channels [20,22].

Electrocardiographic representation of cardiac action potential

The QT interval approximates the duration of the cardiac action potential and is measured from the onset of the QRS complex, which signals the onset of ventricular depolarization, to the end of the T wave, which represents the end of cardiac repolarization. The ST segment, which is the period between the end of the QRS complex and the onset of the T wave, represents the plateau phase of the cardiac action potential. The QRS complex on the surface ECG actually represents the sum of all electrical forces resulting from the spread of cardiac depolarization through the

TABLE 25.2 Ionic currents and their influence on each phase of the action potential.

Ionic current	Cardiac ion channel or membrane protein responsible for the current	Action of ionic current	Phase of ionic current
I_{Na}	Nav1.5 channel	Rapid inward sodium current responsible for depolarization and rising phase of the action potential	Phase 0
I_{to}	KCND2 and KCND3 channel subunits and Kv4.2 or Kv4.3 subunits	Fast transient outward current responsible for repolarization by movement of potassium ions	Phase 1
$I_{Cl(Ca)}$ or $I_{to(2)}$	Ca^{2+}-activated Cl^- channel	Slow transient outward current mediated by movement of chloride ions through calcium-activated chloride channel	Phase 1
I_{NCX}	Sodium–calcium exchanger protein	Sodium–calcium exchanger current governing the plateau phase of the action potential	Phase 2
I_{CaL}	Cav1.2 (L-type calcium) channel	L-type calcium (depolarizing) current governing the plateau phase of the action potential	Phase 2
I_{Ks}	Kv channel with KCNE1 and KCNQ1 subunits	Slow component of the delayed rectifier potassium current especially prominent in supporting repolarization with beta-adrenergic stimulation	Phase 3
I_{Kr}	$K_v11.1$ channel (also known as hERG or I_{Kr} channel)	Rapid component of the delayed rectifier potassium current responsible for the transition from plateau to terminal repolarization	Phase 3
I_{K1}	$K_{ir}2.1$, $K_{ir}2.2$, and $K_{ir}2.3$ channels	Inward rectifier potassium current (an outward repolarizing current) responsible for terminal repolarization of the action potential and sustaining the resting membrane potential of ventricular cardiomyocytes during diastole	Phase 4

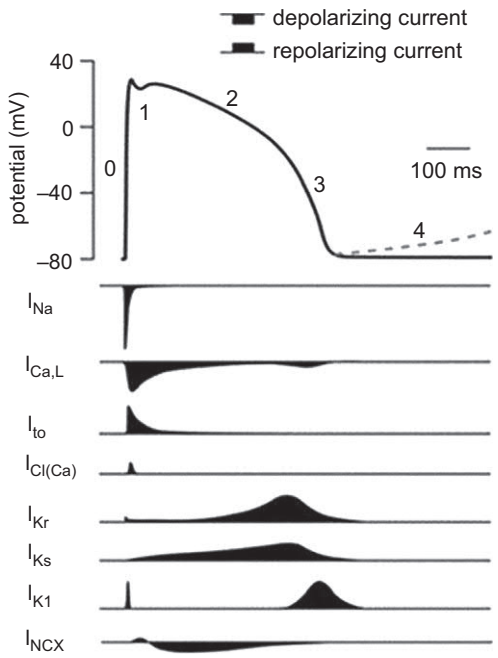

FIGURE 25.1 Representative ventricular action potential (upper panel), along with multiple cardiac ion currents defining cardiac depolarization and repolarization (lower panel). Upward traces for individual ion currents represent outward (repolarizing) current such as hERG; downward traces represent inward (depolarizing) current such as sodium and calcium currents. *Reproduced from Sager PT, Gintant G, Turner JR, Pettit S, Stockbridge N. Rechanneling the cardiac proarrhythmia safety paradigm: a meeting report from the Cardiac Safety Research Consortium. Am Heart J 2014;167(3):292–300 with permission.*

ventricles and is quite narrow since depolarization spreads rapidly via the Purkinje fiber network in the subendocardial region. In contrast, cardiac repolarization is much slower, and its duration varies in different regions of the ventricle, resulting in a broad T wave (Fig. 25.2). Thus, the QT interval represents not only the duration of the cardiac action potential but also the temporal dispersion of the duration of the action potential in different myocardial cells.

Although the QT interval duration, measured from the QRS onset to the end of the T wave, is considered as a surrogate of ventricular repolarization, it can be prolonged due to a conduction defect in the ventricles resulting in a delay in depolarization. Therefore, in an ECG with a wide QRS complex (>100 ms), the JT interval (measured from the end of the QRS complex to the end of the T wave) is often a better surrogate of ventricular repolarization.

Role of potassium channels in drug-induced QT prolongation

Drug-induced prolongation of the QT interval occurs when cardiac repolarization is prolonged by alterations in the function of ion channels responsible for efflux of potassium ions in phase 2 and phase 3 of the action potential, involving the I_{Kr} and I_{Ks} currents [23,24]. The hallmark mechanism of drug-induced QT prolongation associated TdP is the blockade of the I_{Kr} current [25].

The $K_v11.1$ channel that generates the I_{Kr} current is made up of two alpha and two beta protein subunits. Most

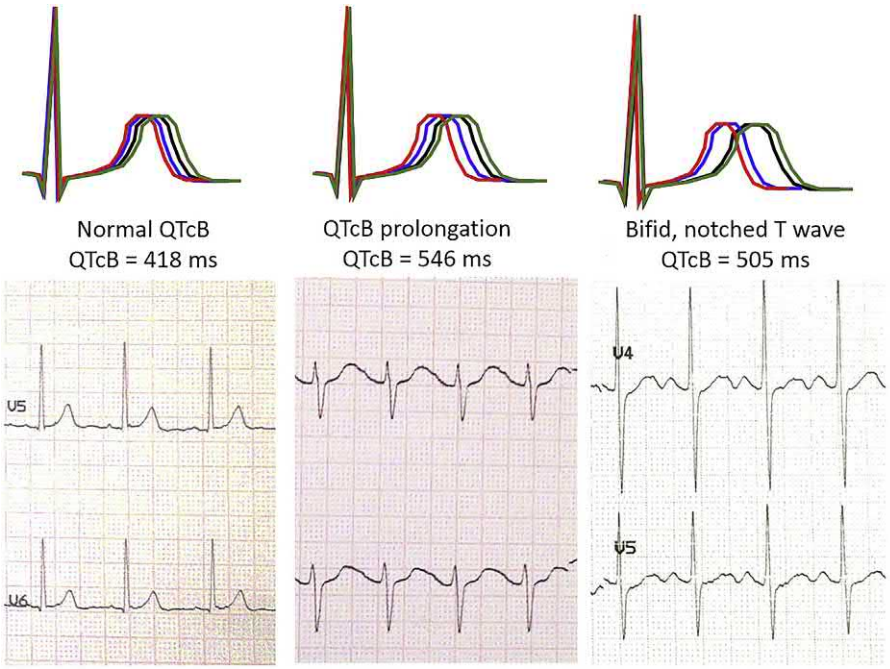

FIGURE 25.2 Stylized representation of cardiac repolarization from different regions of the ventricle contributing toward the duration and morphology of the T wave. The T wave may appear narrow in a normal ECG as the depolarization of different regions of the ventricle differs only slightly. A broad T wave is seen if the duration of depolarization differs widely in different ventricular cells and notched or bifid if there are two regions with widely differing durations of depolarization.

drugs cause QT prolongation by blocking the I_{Kr} current by binding with α subunits in the $K_v11.1$ channel, which is more susceptible to blockade by drugs due to its funnel-like shape with a relatively wide cavity at its intracellular end. The α-subunits in the intracellular pore also have an abundance of aromatic residues (Tyr652 and Phe656) that serve as high affinity binding sites for many drugs [26,27]. In comparison, other potassium channels have a protective mechanism: a proline-X-proline sequence in the S6 domain that reduces the volume of the channel cavity and prevents drugs from being trapped in these channels [28]. As drugs block the $K_v11.1$ channel at its intracellular pore, the offending drugs need to first reach the inside the ventricular myocardial cell. Large molecules like proteins and monoclonal antibodies do not reach the inside of myocardial cells and have therefore not been found to prolong the QT interval [29].

A few drugs like arsenic trioxide and pentamidine inhibit the I_{Kr} current indirectly by abnormal trafficking of proteins that form the $K_v11.1$ channel from their intracellular site of production to the cell membrane. This results in a reduced number of I_{Kr} channels or expression of dysfunctional channels on the cell membrane and reduces the I_{Kr} current resulting in QT prolongation [30].

Role of other channels in aggravating or reducing QT prolongation due to I_{Kr} blockade

Besides the I_{Kr} channel, other ion channels such as the Nav1.5, Cav1.5, and Kv channels also contribute toward balancing or amplifying the effect of drug-induced QT prolongation (Table 25.3) [23]. Upregulation of the Cav1.5 channel for $I_{Ca(L)}$ current prolongs the QT interval, whereas downregulation of the channel shortens phase 2 of the cardiac action potential. Verapamil, a calcium channel blocker, is a potent I_{Kr} current blocker, but it does not cause significant QTc prolongation (except at high concentration levels), because of the concomitant blockade of Cav1.5 channel [31]. Upregulation of I_{Ks}, I_{Kr}, and I_{K1} channel currents can shorten, while downregulation can prolong the QT interval [24]. It is now generally accepted that drugs with effects on multiple cardiac currents, especially those reducing inward (depolarizing) calcium and sodium currents during the action potential plateau, provide protection from proarrhythmia despite a decrease in I_{Kr} current [32–34]. For example, amiodarone causes QT prolongation by about 20% but has a low risk of TdP (<1%) [32].

The concept of repolarization reserve

Patients with drug-induced TdP have greater QT prolongation than those without TdP receiving the same I_{Kr}-blocking drug in similar doses [35] and are at high risk of recurrent arrhythmias if reexposed to the same drug [36]. This variable risk of TdP and drug-induced QT prolongation in different individuals has been explained by the concept of "repolarization reserve." Repolarization reserve implies that a decrease in function of any ion channel involved in the repolarization phase of the action potential may remain subclinical if other pathways are intact [37]. For example, individuals with subclinical congenital long-QT syndrome due to mutations in the genes encoding for I_{Ks} may have a normal QT interval, albeit with a reduced repolarization reserve, if they have a robust I_{Kr}. However, administration of an I_{Kr}-blocking drug to such patients unmasks the defect in I_{Ks} resulting in marked QT prolongation. In contrast, the same reduction in I_{Kr} may produce little change in QT interval in individuals with adequate repolarization reserve. Decrease in repolarization reserve may be congenital or acquired (e.g., myocardial infarction, congestive heart failure, and electrolyte abnormalities). Thus, the framework of repolarization reserve reinforces the general concept that systems controlling important physiologic processes are usually highly redundant and

TABLE 25.3 Heterogeneity of effect of pharmacological agents on action potential in the four predominant cells types found in the ventricular myocardium.

Effect on ion channel	Purkinje	Endocardium	M cells	Epicardium
I_{Kr} block	↑↑↑	↔↑	↑↑↑	↔↑
I_{Ks} block	↔	↑↑	↑↑	↑↑
I_{to} block	↓	↔	↔↓	↔↓
Activation of late I_{Na}	↑↑↑↑	↑↑	↑↑↑↑	↑↑
Activation of I_{Ca}	↑↑↑	↔↑	↑↑↑	↔↑

↔ or ↑, little or no action potential prolongation; ↓, decrease in duration of action potential; and ↑↑, ↑↑↑, and ↑↑↑↑ increasing prolongation effect on action potential.
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therefore assessment of drug-induced QT prolongation must not only be restricted to study of I_{Kr} channel blockade alone but also be extended to other cardiac ion channels.

Reverse use dependency—effect of heart rate

Another important factor that determines the risk of TdP due to drug-induced QT prolongation is reverse use–dependent prolongation of the action potential. The intrinsic rectifying properties of I_{Kr} and I_{K1} decrease disproportionately at lower heart rates, thereby amplifying the effect of I_{Kr}-blocking drugs on ventricular repolarization (Figs. 25.3 and 25.4) [38,39]. Consequently, the risk of TdP is higher with drugs like sotalol that prolong the QT interval and also decrease heart rate [40].

Transmural dispersion of repolarization effect

QT prolongation alone does not predispose to TdP [5] if the action potential is prolonged by the same extent in all myocardial cells, as seen with the antiarrhythmic drug amiodarone. The ventricular myocardium is composed of three electrophysiologically and functionally distinct cell types: epicardial, midmyocardial, and endocardial cells [41]. The number of I_{Kr} and other ion channels vary in cell from these three layers. Most arrhythmogenic drugs prolong the QT interval by different extents in the regions, resulting in what is termed as "transmural dispersion of repolarization" and is seen as broad, low-amplitude T waves that are often deeply notched or bifid (Fig. 25.2) [42]. Appearance of abnormal shape of T waves on the ECG is a sensitive marker of drug-induced I_{Kr} channel inhibition [43], and objective measures of altered T wave morphology like $T_{peak} - T_{end}$ interval have been associated with vulnerability to TdP [42].

Prolongation of the action potential can induce early afterdepolarizations (EADs) due to activation of inward depolarizing currents ($I_{Ca(L)}$ or sodium–calcium exchange current) [44]. EADs occur preferentially in the Purkinje fibers and the midmyocardial M cells and may trigger ventricular premature complexes (VPCs). The presence of increased dispersion of repolarization with varying

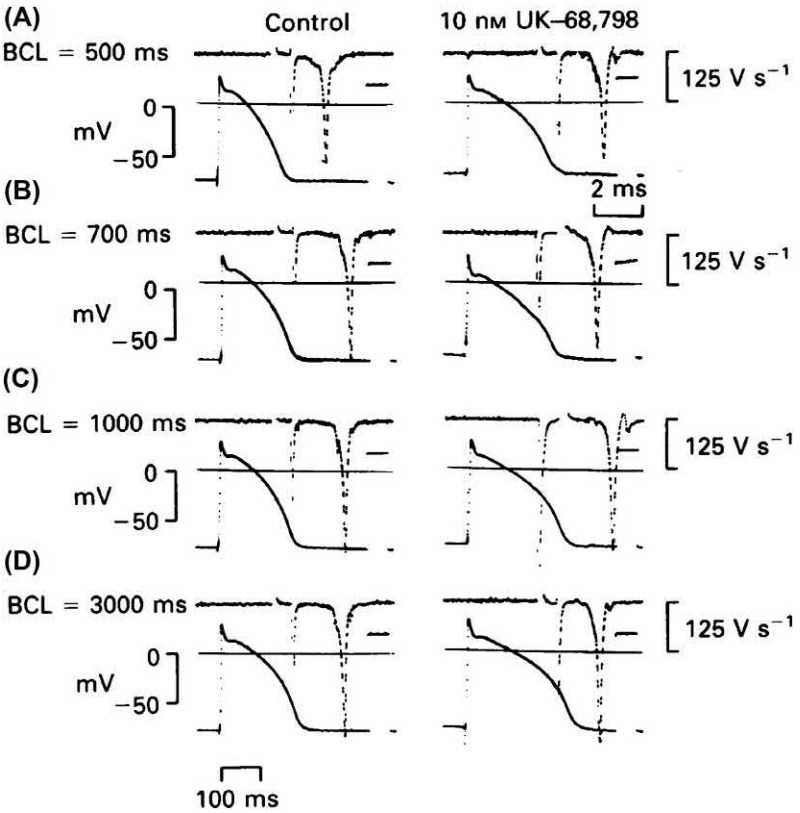

FIGURE 25.3 Reverse rate dependent effect of dofetilide (UK-68,798) at a concentration of 10 nM on the action potential characteristics of dog ventricular muscle stimulated at four different basic cycle lengths (BCL) of 500, 700, 1000, and 3000 ms (corresponding to a heart rate of 120, 86, 60, and 20 beats per minute). Note the progressively greater prolongation of the duration of the action potential and cardiac repolarization at higher cycle lengths (lower heart rates) with UK-68,798 than with control. *Reproduced from Knilans TK, Lathrop DA, Nánási PP, Schwartz A, Varró A. Rate and concentration-dependent effects of UK-68,798, a potent new class III antiarrhythmic, on canine Purkinje fibre action potential duration and Vmax. Br J Pharmacol 1991;103:1568–1572 with permission.*

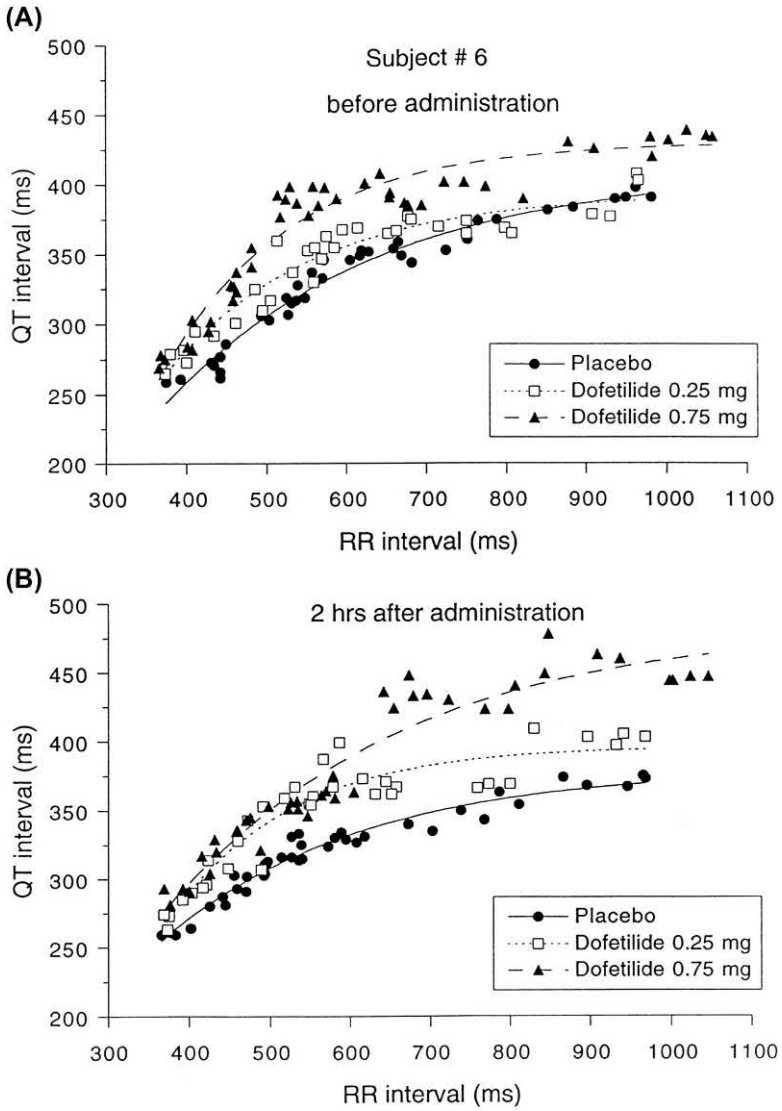

FIGURE 25.4 QT–RR relationship in a healthy volunteer after receiving placebo, dofetilide 0.25 mg or dofetilide 0.75 mg twice daily for 4 days in a crossover study. Note that there was a rate-dependent increase in the QT interval in the placebo period. Dofetilide produced a dose-dependent prolongation of the QT interval. Panel A represents data from Day 4 prior to administration of dofetilide. The QT prolongation was much greater than that with placebo at slower heart rates (higher RR intervals) in Panel B (2 h after dofetilide) demonstrating the reverse use-dependent effect of dofetilide on the IKr channel. *Reproduced from Démolis JL, Funck-Brentano C, Ropers J, Ghadanfar M, Nichols DJ, Jaillon P. Influence of dofetilide on QT-interval duration and dispersion at various heart rates during exercise in humans. Circulation 1996;94:1592–1599 with permission.*

refractory periods in different regions of the ventricle facilitates reentry of the VPCs and provokes TdP, which is then sustained by further reentrant or spiral wave activity [41]. Pentobarbital prolongs the QT interval by inhibiting I_{Kr}, I_{Ks}, and I_{Na} channels. However, its multichannel effect causes greater prolongation of action potential duration (APD) in epicardial and endocardial cells than in M cells, which in turn reduces the transmural dispersion of repolarization resulting in a relatively low risk of TdP [34]. Thus, the incidence of TdP remains low if transmural dispersion is low despite drug-induced QT prolongation.

Regulatory requirements for evaluating drug-induced QT prolongation and proarrhythmic risk

Drug-induced QT prolongation received intense regulatory attention in the 1990s, following reports of drug-induced TdP [45–48] with noncardiac drugs like astemizole, cisapride, grepafloxacin, terfenadine, and terodiline; none of these drugs had been linked to any proarrhythmic liability during drug development [49]. It was also realized that the risk of QT prolongation due these drugs could have been identified by appropriate preclinical testing [50]. This led

the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Agency to issue the first regulatory guidance on assessment of new drugs for drug-induced QT prolongation in 1997 [51]. This was followed in 2005 by the formulation of two important documents by International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): the S7B guidance that addressed preclinical evaluation on QT prolongation liabilities [52] and E14 guidance that dealt with evaluation of proarrhythmic risk based on evaluation of QT interval in humans [53]. Since 2005, the regulatory requirements of a thorough QT (TQT) study outlined in the E14 document have undergone several changes with respect to design, analysis, and interpretation of results and also consideration of alternative strategies based on the experience from several TQT studies [54].

Preclinical evaluation of drug-induced QT prolongation

The recommendations of the CPMP and subsequent discussions resulted in the formulation of the ICH S7A and ICH S7B guidance documents. The ICH S7A guidance deals with the general principles for preclinical evaluation of safety pharmacology of drugs on various organ systems including some cardiovascular safety parameters [55]. Drug-induced QT prolongation was considered important enough to form a separate guidance (the ICH S7B guidance) that discussed in detail use of in vitro and in vivo assays to detect the effect of drugs on ventricular repolarization [52].

ICH S7B guidance

The ICH S7B guidance recommends a series of in vitro patch clamp experiments on native cardiac cells or specific cell lines such as human embryonic kidney 293 or Chinese hamster ovary cells, which have been stably transfected with the gene encoding for the hERG channel in order to quantify the concentration of drug that inhibits the I_{Kr} current by 50%, the IC_{50} [52]. Other in vitro studies include the study of the drug on the APD resulting from the interaction between multiple cardiac ion channels, using multicellular preparations like Purkinje fibers or papillary muscle, ventricular wedge, and Langendorff isolated heart preparations [52]. The ratio of the IC_{50} values estimated from these studies and the effective therapeutic plasma concentration (ETPC) of the free drug would provide an estimate of the margin of safety. IC_{50}/ETPC ratios greater than 50−100 are generally associated with a negative TQT study [56]. The in vivo model consists of evaluating the QT interval and T-wave morphology in ECGs from conscious, freely moving nonrodent animals using telemetric techniques to assess drug effects under more physiological conditions [52].

More recently, the ICH S7B guidance has been criticized for its apparently skewed approach with the detection of even a small effect on I_{Kr} being perceived as having adverse regulatory implications [57]. This has significantly impacted the pharmaceutical discovery pipeline [20,58]. De Ponti estimates that 60% of new molecular entities with potential therapeutic effects have been abandoned early in development for I_{Kr}-blocking liability [59,60]. It is also now recognized that effects of a drug on cardiac channels other than the I_{Kr} channel could also influence the repolarization reserve favorably or adversely. Due to these concerns, there was a need for a more comprehensive approach that takes into account the primary and secondary pharmacology of a drug, differences between results of preclinical studies and human studies, and the effect of a drug on multiple cardiac ion channels that could potentiate or mitigate the proarrhythmic effect of I_{Kr} blockade. The result is the proposed Comprehensive in vitro Proarrhythmia Assay (CiPA) process.

Comprehensive in vitro Proarrhythmia Assay

The US FDA and the Cardiac Safety Research Consortium (FDA/CSRC) aimed to establish new strategies through Think Tank Meetings in 2012 and 2013 [61,62], and a Cardiac Safety Technical Committee was set up to study concordance between preclinical assays and clinical data submitted in support of New Drug Applications. A list of 257 compounds was prepared, of which 150 with high, intermediate, low risk of TdP were identified [63]. Preclinical studies on these compounds have helped develop new models that could better identify potential QT prolonging liability [61].

CiPA has four basic components (Fig. 25.5). The first is the in vitro assessment of drug-induced effects on multiple ionic currents [64], focusing on three dominant currents, namely hERG, late sodium, and calcium currents. Individual ion channel data are then integrated together in the second step in an in silico computer model that generates a model of the action potential in human ventricular myocytes including endocardial, midmyocardial, and epicardial cells and predicts the risk of TdP. When calibrated with drugs from high, intermediate, and low TdP risk categories, this method has been found to provide a reliable measure of proarrhythmic risk. Other in silico strategies include simulation of a pseudo-ECG using multiple ion channel data to estimate the QT prolonging effect and TdP risk [65]. The third component is an in vitro evaluation using human stem cell−derived cardiomyocytes for verifying the findings of the in silico and in vitro ion channel data. The fourth component is the evaluation of QT interval as a biomarker in phase I clinical trials. These four components of CIPA

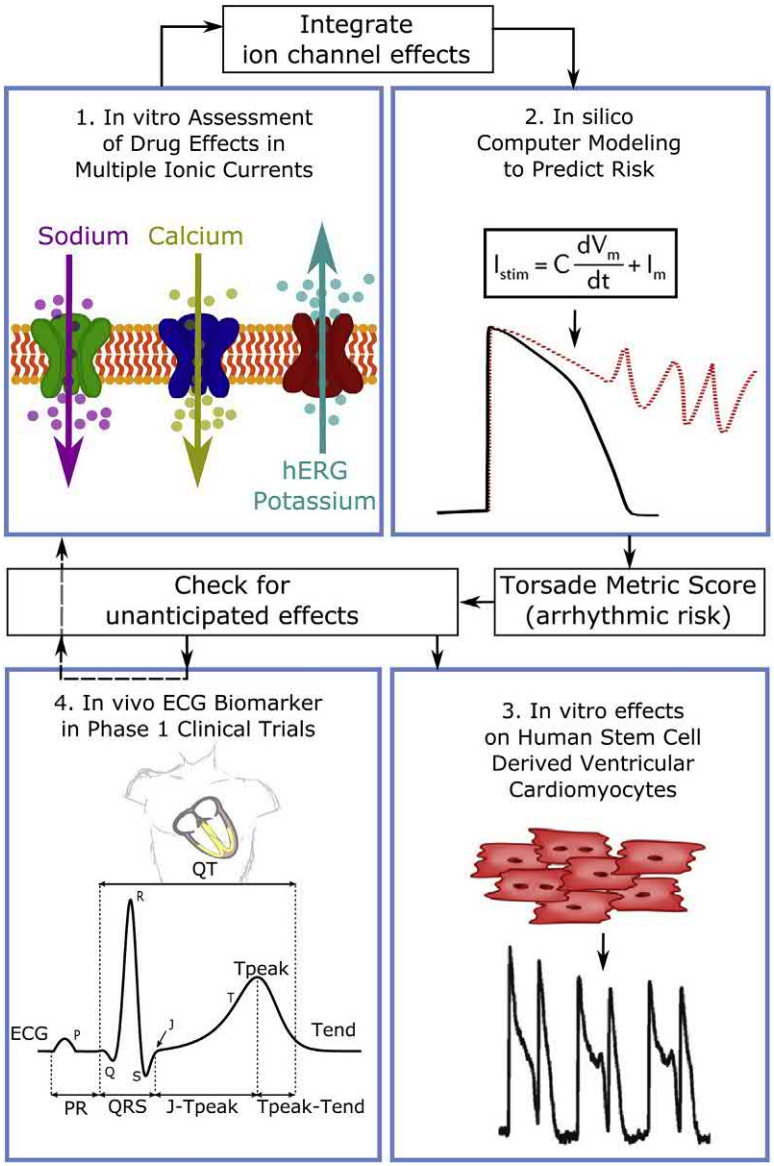

FIGURE 25.5 The four components of the Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative, a new paradigm for assessing proarrhythmic potential of drugs that goes beyond hERG block and QT prolongation. *Reproduced from Vicente J. Update on the ECG component of the CiPA initiative. J Electrocardiol 2018;51(6S):S98–S102 with permission.*

are expected to provide an improved benefit–risk assessment and reduce perceived uncertainty in cardiovascular risk, especially for drugs addressing unmet medical needs [60]. The CiPA methodology has been validated using a set of 28 gold standard compounds chosen to represent a spectrum of multiple electrophysiological mechanisms and belonged to the high, intermediate, or low risk categories. The validation studies have been encouraging, and CiPA is already being implemented in a regulatory setting as an alternative risk assessment pathway for drugs with significant heart rate effects or other factors that confound QTc assessment [64]. The CiPA also involves a fourth component of clinical testing, which is to be interpreted along the preclinical data and is discussed in more detail below.

Clinical evaluation of drug-induced QT prolongation

ICH E14 guidance and TQT study

Since 2005, the ICH E14 guidance requires all new drugs with systemic effects to undergo a TQT study to detect any potential drug-induced QT prolongation effect prior to

seeking regulatory approval [53]. A TQT study is typically conducted in healthy volunteers and has four treatment arms—two treatment arms of the investigational drug (one receiving the therapeutic dose and the other receiving a supratherapeutic dose), one negative control treatment arm (placebo) and a positive control treatment arm receiving a drug known to prolong the QT interval (usually moxifloxacin). Digital 12-lead ECGs are recorded in subjects at prespecified baseline and postdose time points that are determined by the T_{max} and other pharmacokinetic properties of the drug [66].

The primary endpoint of the study is the change from baseline in the QT/QTc interval after administration of the study drug. As there is considerable circadian variation in the QT interval, postdose changes are adjusted for time-matched change from baseline observed in the placebo arm (Fig. 25.6) [67]. The TQT study is considered negative if the 95% one-sided upper confidence bound of the

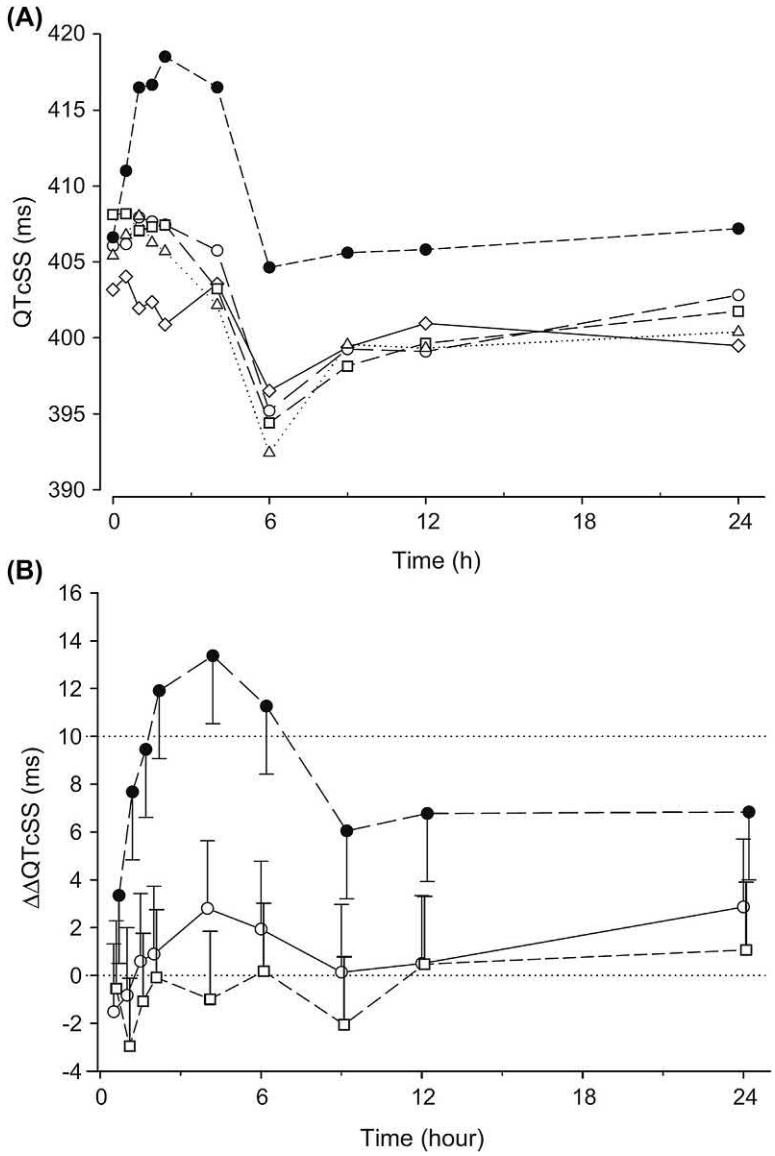

FIGURE 25.6 Results from a four-way crossover design thorough QT study with placebo, levocetrizine 5 mg, levocetrizine 30 mg, and moxifloxacin 400 mg (positive control) in 52 normal healthy subjects. Panel A shows mean QTc interval (QTcSS) at various time points over 24 h after dosing. Note the marked diurnal variation in the QTc interval in the placebo group, which is also seen in the levocetrizine treatment groups. Panel B shows placebo-adjusted change from baseline in QTc (ΔΔQTcSS) in the levocetrizine and moxifloxacin treatment groups. Note the QT prolongation with moxifloxacin, which peaks at 4 h, and the absence of QT prolongation with both doses of levocetrizine with the upper bound of the 95% one-sided confidence interval below 10 ms at all postdose time points. *Reproduced from Hulhoven R, Rosillon D, Letiexhe M, Meeus MA, Daoust A, Stockis A. Levocetirizine does not prolong the QT/QTc interval in healthy subjects: results from a thorough QT study. Eur J Clin Pharmacol 2007;63:1011−1017 with permission.*

placebo-adjusted QTc prolongation after drug administration is < 10 ms at all time points at which ECGs are recorded [53,66]. To demonstrate that the study methodology was robust and reliable, a similar analysis should be able to demonstrate the QT prolonging effect with the active control drug (Fig. 25.6).

A classical TQT study may not be feasible for certain drugs such as oncologic drugs as they may be too toxic to be given to healthy volunteers. The use of a placebo treatment arm (alone) may be unethical in cancer patients. In these cases, an alternative approach is to conduct an intensive QT evaluation study in which patients with cancer are being treated for their disease with a currently accepted regimen. The study drug is often added on to the ongoing medications, and ECGs are recorded and analyzed as in a TQT study. Similarly, a traditional approach may not be optimal for macromolecules such as therapeutic proteins since these drugs have long half-lives often in weeks. Rodriguez and colleagues have suggested alternative potential approaches in development programs of therapeutic proteins [68].

Since its implementation in 2005, an assessment of the FDA regulatory decisions database for TQT studies, between 2006 and 2013, showed that 46 drugs out of the 205 NDA submissions were identified as QT prolonging drugs [69,70]. Forty one of these 46 drugs were approved with appropriate labeling restrictions such as boxed warnings, contraindications and precautions, and detailed descriptions of adverse reactions in the package insert [71]. Thus, the TQT study has made drug safety labeling more objective and informative. The greatest success of the ICH E14 guidance has been that no new drug approved for marketing after 2005 has been withdrawn due to an unanticipated risk of TdP or SCD [66].

Limitations of the ICH E14 guidance

Although the TQT study has been successful in detecting drug-induced QT prolongation during the drug development stage, its success has paradoxically impacted the development of new drugs as pharmaceutical companies have become overcautious while considering drugs with potential QT liability for further development. A TQT study, costing \$2−3 million, is mandated for all drugs, even if no effects on the I_{Kr} channel are found in preclinical studies. This is seen as a major financial burden, especially for pharmaceutical start-ups. The likely therapeutic dose of the study drug is usually decided at the end of phase 2. Therefore, TQT studies are usually conducted just prior to phase 3 of clinical development. The need to conduct the TQT study in late phase 2 or early phase 3 means that substantial costs have already been incurred before the TQT study is performed and having to abandon a drug at this late stage is financially challenging. Apprehension regarding regulatory hurdles that could be encountered at later stages of drug development has also resulted in several potentially promising drugs being discontinued in the development pipeline by the pharmaceutical company. These concerns explain why the number of positive TQT studies has declined from 60% in 2005 to 10% in 2012 [70].

Concentration-QTc (PK-PD) modeling—its evolution and IQ-CSRC study

Concentration-effect modeling using data from a TQT study to study the relationship between plasma drug concentration and QTc prolongation was introduced in 2008 to complement the traditional by-timepoint analysis described in the ICH E14 guidance. Due to good concordance between results from concentration-QTc modeling and from by-time analysis of the placebo-adjusted change in the QTc interval in many TQT studies, concentration-QTc modeling has gained widespread acceptance [69]. It helps exclude misinterpretation of results for a new drug that shows marginal QTc prolongation at a single time point as a type I statistical error. Concentration-QT evaluation also takes into account individual responses instead of averaging the QT response at each time point [71]. It can help in predicting QT prolongation with doses other than those used in a TQT study. Concentration−QTc analysis also allowed quantification of incremental risk in special populations such as patients with hepatic insufficiency [72] and in subjects is with high plasma drug concentrations [73].

Concentration-effect analysis has another major advantage. It can be used in early phase studies where a small number of volunteers receive ascending doses of a new drug, and plasma concentrations of the drug achieved are often higher than those in TQT studies. Due to the small sample size ($n = 6−8$ subjects), these early phase studies are statistically underpowered to demonstrate a placebo-adjusted change in mean QTc as described in the ICH E14 guidance. However, as shown by a recent study by the International Consortium for Innovation and Quality in Pharmaceutical Development and the Cardiac Safety Research Consortium (IQ-CSRC study), it is possible to detect drug-induced QTc prolongation with a limited number of healthy subjects using concentration-QTc modeling [74]. It is now being proposed that concentration-QTc model derived estimates of drug-induced QT prolongation from well-designed phase 1 studies with intensive ECG recording and analysis could be used to request for a regulatory waiver for the TQT study.

Although attractive, this study methodology has its own set of limitations. The study is conducted during early phase clinical development when clinically relevant plasma concentrations of the drug and its metabolites are not known and the doses studied may sometimes be lower than the eventual therapeutic dose. The choice of ECG time

points is often limited by lack of knowledge of pharmacokinetics of the new drug and active metabolites in humans. Concentration-QTc modeling for drugs/metabolites with long half-lives will multiple ascending dose studies. Pooling data from multiple studies will increase sample size but may introduce other confounding factors. Assessment of drugs with prominent heart rate effects, poor tolerability in healthy volunteers, and drugs that prolong QT by mechanisms other than hERG channel blockade (e.g., hERG receptor trafficking) could be challenging [58].

Postmarketing evaluation of drug-induced QT prolongation

The value of postmarketing evaluation of drugs for adverse cardiac effects was highlighted with rofecoxib, a COX-2−selective inhibitor that was found to be strongly associated with increased risk of myocardial infarction. Similarly, azithromycin received marketing approval in 1991 and its propensity to prolong the QT interval was first reported in 2001 [75]. A study published in 2012 in the *New England Journal of Medicine* showed an increase in cardiovascular deaths and death from any cause in patients treated with azithromycin as compared to those treated with amoxicillin, ciprofloxacin, or no drug [76]. In March 2013, the US FDA issued a new warning on the use of azithromycin stating that it can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal cardiac arrhythmia [77]. Postmarketing data of rare adverse events accumulated over several years have resulted in withdrawal of drugs such as propoxyphene, cisapride, thioridazine, droperidol, and sparfloxacin [69].

Widespread use of electronic medical records (EMR), "big data" analytics, and advances in data science are set to make important contributions to pharmacovigilance, especially for rare adverse effects like TdP, where association with specific drugs can only be made after millions of patients have been treated with the drug. Concomitant medications usually make this association more difficult, leading Roden et al. to compare this process to "looking for the proverbial needle in the haystack." [78] Using EMRs, Castro could confirm that the antidepressant citalopram is associated with QT interval prolongation [79]. Loberbaum et al. used a combination of data mining approaches to identify that the drugs ceftriaxone and lansoprazole, which individually have no QT "signal," were associated with QT prolongation when administered in combination. The authors subsequently confirmed this by in vivo and in silico electrophysiological studies [78,80]. It is likely that data mining strategies like these could lead to identification of other combinations of drugs that could be associated with rare adverse effects. However, Hauben et al. caution against the "tendency to conclude that, with large enough datasets and intricate algorithms, the numbers speak for themselves." [81] While advances in data science can help identify potential adverse drug interactions, these associations should be confirmed by appropriate in vitro and in vivo studies.

Risk mitigation strategies for QT prolonging drugs

Presently, several drugs with QT prolongation liability are still marketed. The Arizona Center for Education and Research under a contract with the FDA's Safe Use Initiative maintains a web-based list of drugs that have a risk of QT prolongation and/or TdP, which is available on the CredibleMeds website [82]. CredibleMeds places drugs in four categories of TdP risk. Drugs with "known risk of TdP" have convincing evidence that they can cause TdP, even when administered as recommended on the drug's FDA label (Table 25.4). Drugs that prolong the QT interval during routine clinical use, but with no convincing evidence of TdP causality, are classified as having a "possible risk of TdP." A "conditional risk" category includes drugs for with a risk of TdP, but only under certain specific conditions, such as overdose, hypokalemia, hypomagnesemia, bradycardia, or with interaction with another drug. A fourth category lists drugs to be avoided by patients with congenital LQTS. CredibleMeds has become an invaluable tool and its use has probably saved many lives. Physicians prescribing these drugs should be careful in selecting the right patients, avoiding concomitant medications that could worsen the QT prolongation, and prevent electrolyte disturbances. Monitoring the QT interval at baseline and while on treatment could help discontinue the medication before the occurrence of potentially fatal arrhythmias (Fig. 25.7).

Differences in drug-induced QT prolongation in men and women

The incidence of drug-induced QT prolongation has shown notable sex-related differences with a significant female predisposition [83]. Studies have revealed that drug-induced QT prolongation occurs more frequently in women and also the extent of prolongation is greater than in men. Also, more women with drug-induced QT prolongation develop TdP than men [12]. A study in Germany by Sarganas et al. has estimated the incidence of drug-induced QT prolongation to be 2.5 per million person years in men and 4.0 per million person years in women [16]. In another retrospective study, Molokhia et al. estimated the incidence to be 10.9 per million person years (95% confidence interval 7.8, 14.8) in women, with a higher susceptibility to

TABLE 25.4 Drugs associated with TdP. Of the 266 drugs possibly associated with TdP as per the AZCERT, only 55 drugs classified as "Known risk of TdP" defined as "Substantial evidence supports the conclusion that these drugs prolong the QT interval AND are clearly associated with a risk of TdP, even when taken as directed in official labeling" are listed here in alphabetical order.

Aclarubicin	Erythromycin	Oxaliplatin
Amiodarone	Escitalopram	Papaverine HCl (intracoronary)
Anagrelide	Flecainide	Pentamidine
Arsenic trioxide	Fluconazole	Pimozide
Astemizole	Gatifloxacin	Probucol
Azithromycin	Grepafloxacin	Procainamide
Bepridil	Halofantrine	Propofol
Chloroquine	Haloperidol	Quinidine
Chlorpromazine	Hydroquinidine (dihydroquinidine)	Roxithromycin
Cilostazol	Ibogaine	Sevoflurane
Ciprofloxacin	Ibutilide	Sotalol
Cisapride	Levofloxacin	Sparfloxacin
Citalopram	Levomepromazine (methotrimeprazine)	Sulpiride
Clarithromycin	Levomethadyl acetate	Sultopride
Cocaine	Levosulpiride	Terfenadine
Disopyramide	Mesoridazine	Terlipressin
Dofetilide	Methadone	Terodiline
Domperidone	Moxifloxacin	Thioridazine
Donepezil	Ondansetron	Vandetanib
Dronedarone		
Droperidol		

Based on Woosley RL, Romero KA. Crediblemeds.org QT drugs List, 2019. AZCERT, Inc. Available at: https://crediblemeds.org. [Accessed 16 August 2019].

TdP in women [15]. In a metaanalysis of 332 patients, 70% of patients who developed drug-induced QT prolongation and TdP were women [12]. Higher incidence of drug-induced QT prolongation has been observed with antiarrhythmic drugs [35,84] and with noncardiovascular drugs like terfenadine [85], erythromycin [86], cisapride [87], and probucol [88]. Increased incidence of QT prolongation in women has been observed with quinidine (14.3% vs. 4.4% in men) [89], sotalol (relative risk of 4.7 vs. 1.5 in men) [90], and dofetilide. A study based on concentration-QT modeling in men and women administered a single oral dose of dl-sotalol showed that women had a higher baseline QTcF value than men. Furthermore, the slope of the concentration-QTc relationship was steeper in women than in men implying that women had greater QT prolongation at any plasma concentration of a drug than men, and equivalent increments in plasma concentration would produce greater increase in the QT interval in women [91].

Sex-related differences in cardiac repolarization and electrophysiology

The increased propensity to drug-induced QT prolongation in women is attributed to the numbers and proportions of various cardiac ion channels in the myocardium and the effects of sex hormones on the functioning of these ion channels [92]. Animal studies have shown that male mice have larger ultrarapid delayed rectifier K^+ current (I_{Kur}) and expression of the underlying α-subunit Kv1.5, with male mice having shorter QT intervals than females [93]. In orchidectomized mice, the I_{Kur} current is smaller and the expression of the Kv1.5 is reduced, resulting in prolonged QTc interval which is normalized after administration of androgens [94]. Similarly, the QT interval is shorter in male dogs, and testosterone increases the inward I_{K1} and transient outward I_{to} K^+ currents, along with Kir2.1 and Kv4.3 subunit expression [95]. Estrogen administration decreases

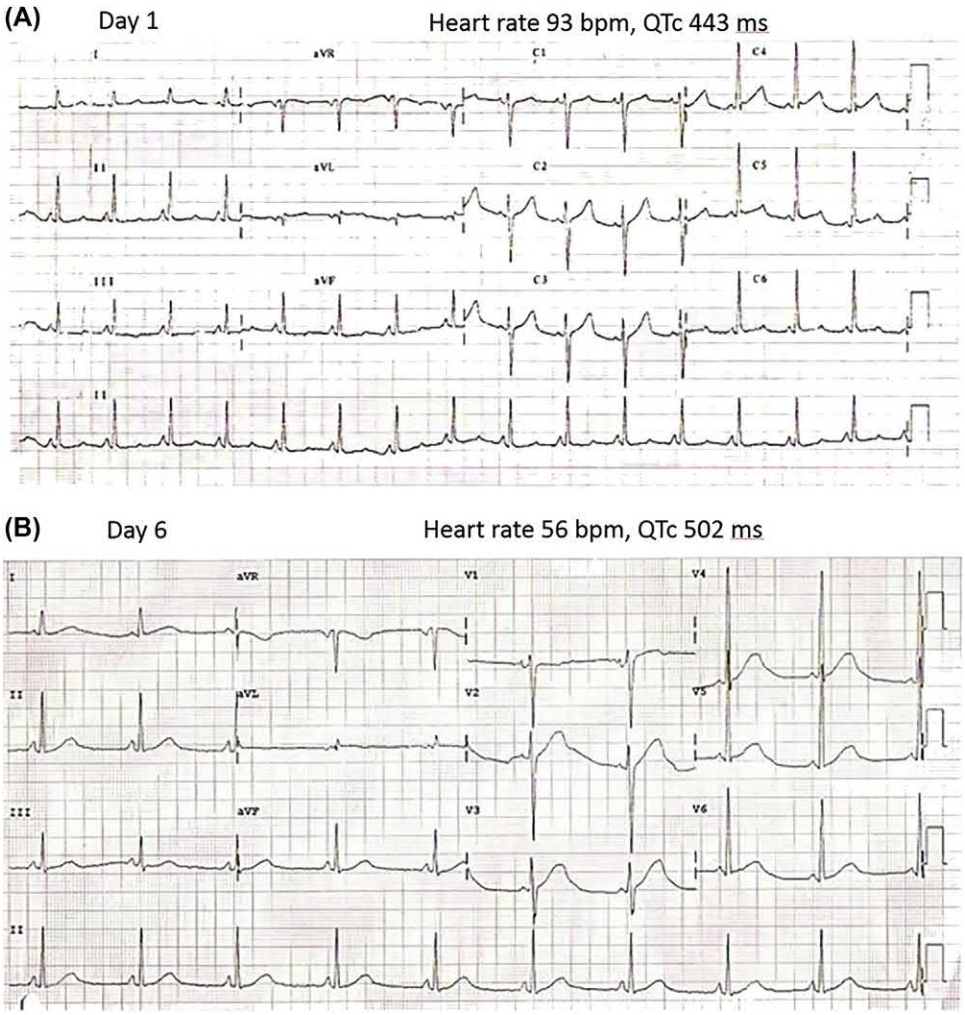

FIGURE 25.7 12-lead ECGs from a 35-year-old male patient with severe falciparum malaria who was treated with intravenous quinine. Panel A: Baseline ECG before starting quinine. Panel B: ECG on Day 6 of treatment shows prolonged QT interval with a broad T wave. The dose of quinine was reduced by 50%. The QTc interval returned to normal on Day 7.

the inward I_{K1} and transient outward I_{to} K^+ currents in male dogs and prolongs the QT interval. Female dogs have also been found to have fewer I_{to} channels and a larger I_{CaL} current, with reduced repolarization reserve [96]. In guinea pigs, administration of high-dose testosterone shortens the QT interval by increasing I_{Ks} and reducing I_{CaL} currents [97].

Human data on cardiac ion channels and their expression are in general agreement with animal studies. Adult women have lower levels of expression of hERG and other K^+ channel subunits like β-subunit of I_{Ks} and thus smaller repolarization reserve. Sex-related differences in the QT interval differ with age. There is a marked QTc interval shortening in male neonates and infants between 1 and 3 months due to the activity of the hypothalamic–pituitary–gonadal axis in this period resulting in a higher level of testosterone in males [24]. This is followed by a period where there is no significant difference in QTc interval values between males and females till puberty [24]. At puberty, production of testosterone in males and estrogens in females increases rapidly resulting in a marked separation between the QT interval values in males and females. After puberty, the QTc interval in males shortens by about 20 ms, while it remains unchanged in females [98]. This postpubertal difference persists through adulthood, with the QTc interval gradually increasing with age in both sexes (Fig. 25.8) [24]. With a gradual decline in testosterone levels in males, the difference in QTc between men and women decreases after the age of 50 years.

Administration of gonadotropin-releasing hormone antagonists such as abarelix, leuprolide, and goserelin significantly prolong the QT/QTc interval in men by reducing androgen levels when used in treatment of prostate cancer. Bidoggia et al. noted that castrated men had a

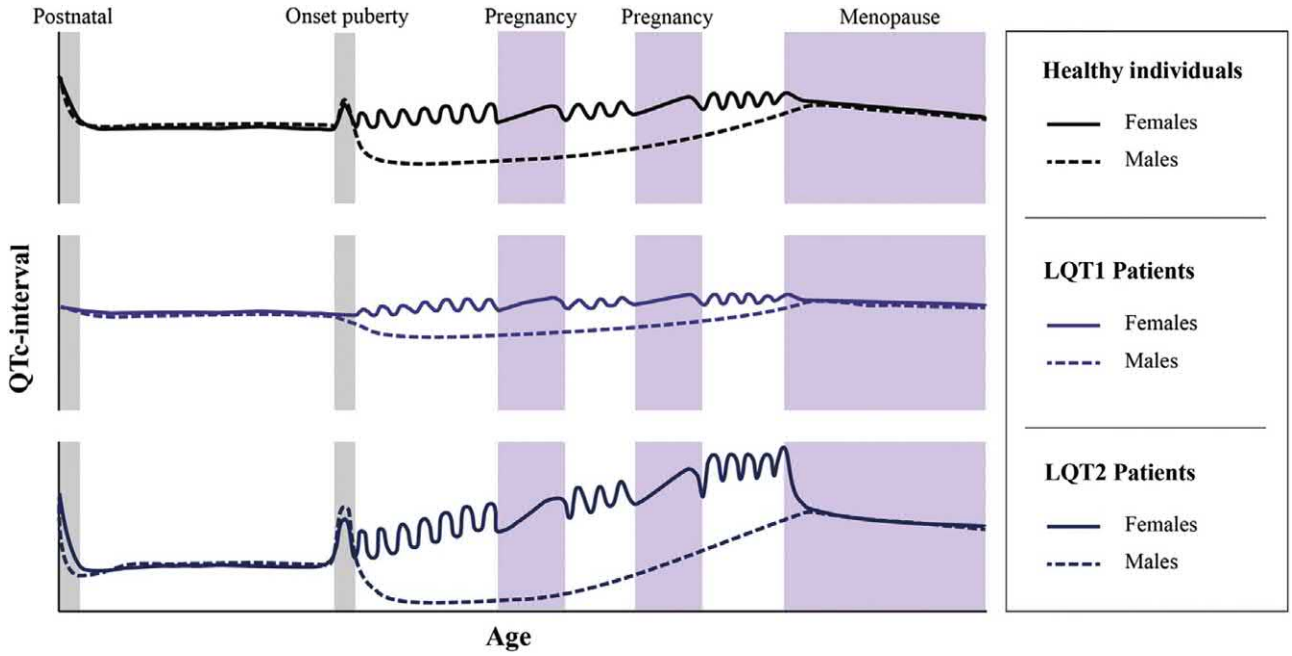

FIGURE 25.8 Schematic representation of hypothetical changes in the QTc interval with age in healthy males and females and patients with congenital long-QT syndromes (LQT1 = long-QT syndrome Type 1; LQT2 = long-QT syndrome Type 2). *Reproduced from Vink AS, Clur SB, Wilde AAM, Blom NA. Effect of age and gender on the QTc-interval in healthy individuals and patients with long-QT syndrome. Trends Cardiovasc Med 2018;28(1):64–75 with permission.*

longer QTc interval than did noncastrated men. This study also found that women with a virilization syndrome had shorter QTc intervals than did castrated men and healthy women [99]. Thus, orchiectomy reverses the sex differences and increases the incidence of I_{Kr} blocker–induced EADs, and ovariectomy has the opposite effect.

The importance of QT prolongation with age is also underscored by a threefold increase in cardiovascular events in elderly men with a QTc greater than 420 ms [100] and a twofold increase in drug-induced QT prolongation and sudden death in older men receiving antipsychotic drugs. Other repolarization abnormalities like early repolarization, idiopathic VF, and Brugada syndromes may also occur more commonly in men than in women probably related to hormonal influence on cardiac ion channels (Fig. 25.9). [92].

Role of sex hormones on the QTc interval and drug-induced QT prolongation in women

Sex hormones seem to modulate cardiac repolarization by their effects on $I_{Ca,L}$, I_{Kr}, I_{Ks}, and I_{K1} channel currents. Both animal and human studies have shown that testosterone decreases the $I_{Ca,L}$ current and increases the potassium channel currents, resulting in shorter QTc interval values in adult males. In females too, progesterone decreases the $I_{Ca,L}$ current and increases the I_{Ks} current and shortens the QTc interval [101]. In contrast, estrogens decrease potassium channel currents and prolong the QT interval only in animal studies. In human, estrogens have shown varying effects on QTc interval with different studies showing an increase, decrease, or no change in the QT interval. In postmenopausal women, estrogen replacement therapy produced QT prolongation, whereas hormone replacement therapy with estrogen plus progesterone had no effect on the QT interval [102]. Additionally, women show estrogen-dependent upregulation of Na^{+}–Ca^{2+} exchanger and I_{CaL}, which favor EADs and TdP [92].

The effects of cyclical changes in estrogen and progesterone levels on QT interval in premenopausal women are complex. Estrogen and progesterone levels are lowest at the onset of menstrual periods. After cessation of menstrual flow, there is a gradual increase in estrogen during the follicular phase with estrogen levels peaking in the middle of the menstrual cycle during ovulation. After ovulation, the estrogen levels gradually decrease during the luteal phase. In contrast, progesterone levels are low during the follicular phase and increase after ovulation through the luteal phase [92] (Fig. 25.10).

In healthy females, the QTc interval does not differ between the different phases of the menstrual cycle. However, on evaluation of the QTc interval after autonomic blockade, Burke et al. found the average QTc interval (438 ± 16 ms) was shorter in the luteal phase than during the menstrual (446 ± 15 ms) and follicular phases (444 ± 13 ms) suggesting that autonomic tone is an

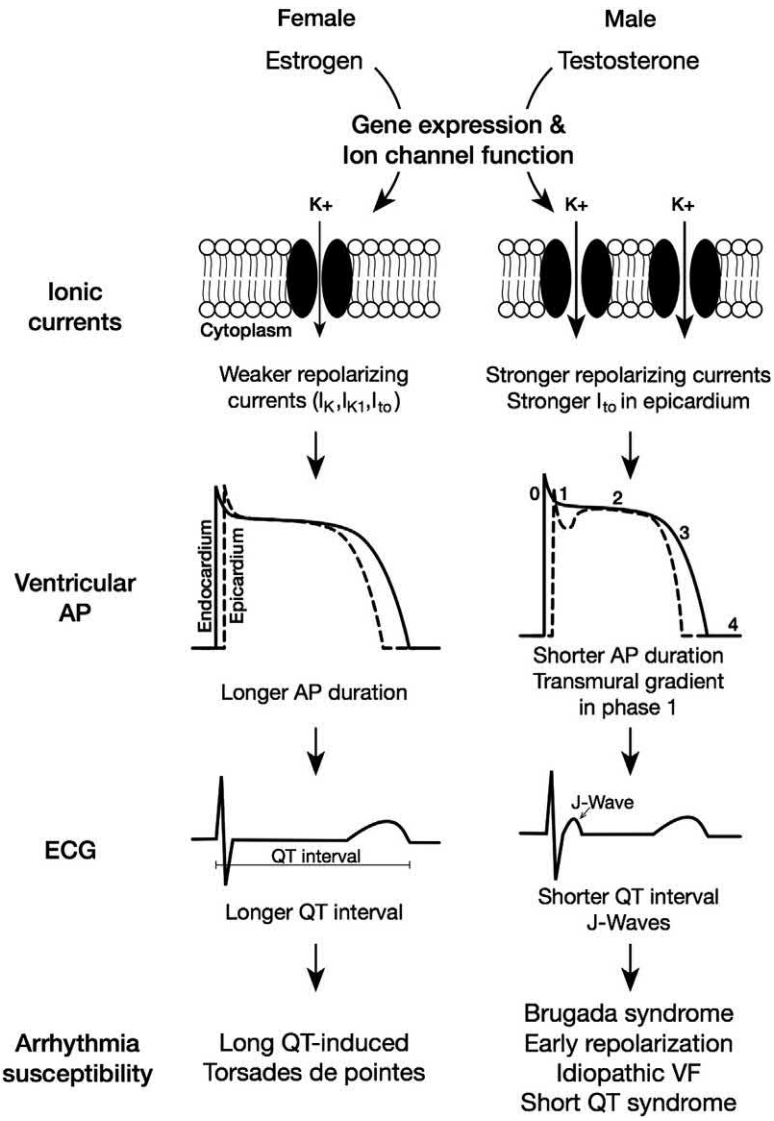

FIGURE 25.9 Physiological basis of the higher risk of long QT–associated arrhythmias in women and early repolarization, idiopathic ventricular fibrillation, and Brugada syndromes in men. *Reproduced from Tadros R, Ton AT, Fiset C, Nattel S. Sex differences in cardiac electrophysiology and clinical arrhythmias: epidemiology, therapeutics, and mechanisms. Can J Cardiol 2014;30(7):783–792 with permission.*

important factor influencing the QTc interval during the menstrual cycle [9,92]. Drug-induced QTc interval prolongation after ibutilide (an I_{Kr} blocker) infusion is greatest during menstruation and the ovulatory phase as compared to the luteal phase indicating an exaggerated susceptibility to drug-induced arrhythmias when the estrogen level is highest [103]. This increased susceptibility to QT prolongation has also been seen during estradiol treatment, and treatment with an estradiol and progesterone combination reduces risk of drug-induced arrhythmias [104]. Hormone levels may also influence cytochrome P4503A (CYP3A) expression, which is a major metabolic pathway for clearance of many I_{Kr}-blocking drugs like erythromycin, clarithromycin, ketoconazole, itraconazole, cisapride, droperidol, pimozide, sildenafil, thioridazine, and domperidone and may play some role in the greater drug-induced QT prolongation seen in females [105].

Summary and conclusions

Drug-induced QT prolongation is commonly encountered during drug development, and the regulatory framework for evaluation of proarrhythmic effects of new drugs is clearly defined and has been very effective in identifying these drugs. However, a paradigm shift is taking place in the preclinical and clinical evaluation of drug-induced QT prolongation. The new strategy of CiPA for preclinical studies and concentration-QTc modeling in early phase

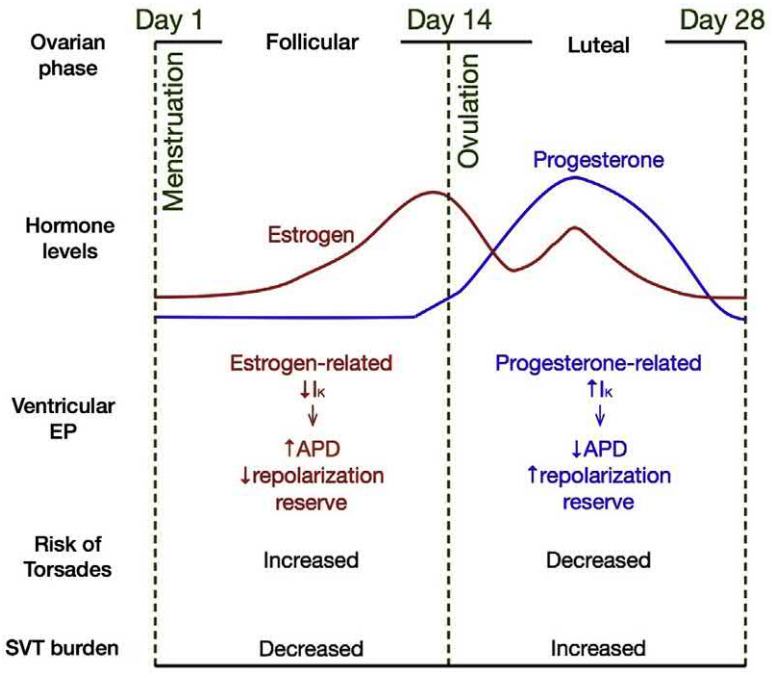

FIGURE 25.10 Female ovarian cycle with related hormonal and electrophysiological changes. *Reproduced from Tadros R, Ton AT, Fiset C, Nattel S. Sex differences in cardiac electrophysiology and clinical arrhythmias: epidemiology, therapeutics, and mechanisms. Can J Cardiol 2014;30(7):783–792 with permission.*

human studies is still in its infancy and may ultimately replace the present regulatory framework. Meanwhile, several drugs with a QT prolonging effect are still in clinical use including antipsychotics, antibacterial and antifungal agents, and oncology drugs. The CredibleMeds website has a comprehensive list of these drugs and one should be careful when prescribing these medicines. It is important to evaluate the baseline QTc interval, avoid concomitant medicines that could exaggerate the QTc effect by interaction at the cardiac ion channel or on drug metabolism, prevent electrolyte imbalance, avoid use in patients with underlying heart disease or congenital LQTS, and frequently monitor QTc interval while on medication.

Adult females have a longer baseline QTc interval than males. This is because the QTc interval shortens in males between puberty and climacteric due to the effect of testosterone. Consequently, females seem to be more predisposed to develop drug-induced QTc prolongation and the frequency and severity of drug-induced QT prolongation is higher in females than in males at the same serum concentration of a drug. The effects of estrogen and progesterone on the QT interval are more complex. Nevertheless, female sex seems to be an important predisposing factor for developing TdP, a rare but potentially fatal cardiac arrhythmia that often follows drug-induced QT prolongation.

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Chapter 26

Mechanisms and incidence of torsades de pointes tachycardia

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Introduction

The term "torsades de pointes" (TdP) was first established by French cardiologist François Dessertenne in 1966 [1]. He used it for description of a specific polymorphic ventricular tachycardia (VT) with continuously changing morphology of the QRS complexes that look like twisting around an isoelectric baseline. In French, TdP means something like "spiral twisting of points." In the literature, the term is very often misspelled for "torsades des pointes" or "torsade des pointes". "Torsades" is a plural of "torsade" and both expressions are used in French texts. While "de" is a preposition used for expression of the genitive case (similar to "of" in English), "des" is an indefinite article in plural.

Although all cardiologists are using the term TdP, there is no precise definition of this tachycardia. In the literature, it often refers to various forms of polymorphic VTs. Some authors recommend to speak about TdP only in relationship to QT interval prolongation, while others refer to polymorphic VT initiated by a late extrasystole [2,3]. Morphologically, the change of QRS complex morphology and amplitude should be gradual (Fig. 26.1). Nevertheless, even in patients with both congenital and acquired long-QT syndrome (LQTS), different VT patterns can be present (Fig. 26.2). The uncertainty in TdP definition is at least partially caused by uncertainty in understanding of its mechanisms.

Mechanisms

In majority of cases, TdP is associated with QT interval prolongation and its occurrence with normal QT interval is extremely rare. Study of this VT has been promoted by tremendous progress in the field of cardiac channelopathies. Since 1990s, these syndromes have served as a model of arrhythmogenesis.

A prolonged QT interval on the surface electrocardiogram is a surrogate of prolonged ventricular action potential (AP) duration. The AP duration lengthening leads to the following: 1. dispersion of repolarization (being n-onhomogenous across the ventricular wall) and 2. to AP oscillations called early afterdepolarizations (EADs). These conditions form the substrate of TdP [2]. Association of EADs with TdP was proposed in the beginning of 1980s [4–7], and since then, these phenomena have been attracting continuous interest and articles reviewing the topic are published regularly in electrophysiological journals (the last ones not later than in 2018) [8,9].

Early afterdepolarizations

Despite the long history of EADs research, their understanding remains incomplete. Descriptively, the EADs are oscillations in membrane potential that follow the primary depolarization of an AP before the repolarization is completed (on the contrary to delayed AD, which occurs after the end of AP).

Generally, a depolarization is caused by some inward current. Under normal conditions, channels underlying such currents have concluded their role in AP formation before the beginning of repolarization during which they have not recovered yet. But, when repolarization time is prolonged, these channels can reach recovery, may reopen, and generate inward currents again. The L-type Ca current ($I_{Ca,L}$) and the Na−Ca exchange current (I_{NCX}) are the major currents with potential to create EADs.

Under physiologic conditions, activation of $I_{Ca,L}$ current decreases as the cell repolarizes. Nevertheless, when repolarization time is prolonged, I_{CaL} can partly recover and continue to generate an inward current. This current can depolarize the membrane potential causing an EAD.

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FIGURE 26.1 Polymorphic ventricular tachycardia torsades de pointes of a typical morphology with gradual changes of QRS complex amplitude and morphology.

The second major current that can play role in EAD formation is I_{NCX}. The cardiac Na−Ca exchanger produces an inward current when exchanging three Na ions for one Ca ion to remove calcium from the cytoplasm. As calcium is released from the sarcoplasmic reticulum during the process of activation−contraction coupling, cytosolic calcium concentration temporarily increases with a subsequent sudden activation of the I_{NCX} inward current. Importantly, $I_{Ca,L}$ and I_{NCX} are such highly interactive currents that it is hardly possible to differentiate whether one or the other causes EADs [10].

Both I_{CaL} and I_{NCX} density and activity are influenced by sex hormones that may thus contribute to sex differences in the susceptibility to triggered activity. Majority of data has been obtained from animal studies that must be interpreted with caution. For example, rodents have different repolarization characteristics lacking many of sex differences observed in humans, while rabbit's cardiac repolarization characteristics are similar to those of humans including sex differences. Although the net overall effects of sex hormones on calcium handling and triggered activity are hard to predict (comprehensive studies are lacking), it is quite clear that female sex, in general, and specifically estradiol may increase the propensity for triggered activity, while testosterone and progesterone may reduce its likelihood [11]. However, the topic is discussed in detail in other chapters of this book.

There is still some uncertainty concerning the mechanism causing the continuation of triggered APs following the first one triggered by the EAD. Probably, it is possible due to the fact that cells are coupled together by gap junctions that minimize AP duration differences between adjacent cells [12].

Perpetuation of TdP

The mechanism of TdP perpetuation is still under debate. This topic has been studied on animal models and using computer modeling, and two hypotheses have been proposed. First, TdP might be explained by competing foci of multiple simultaneously triggered cells. This multifocal model might easily explain the polymorphic characteristic of TdP. Another possibility is reentry. The typical TdP pattern is then caused by transient bifurcation of a predominantly single rotating wavefront into separate simultaneous wavefronts rotating and drifting around both ventricular cavities. Important feature of TdP reentry mechanism is the fact that on the contrary to anatomical

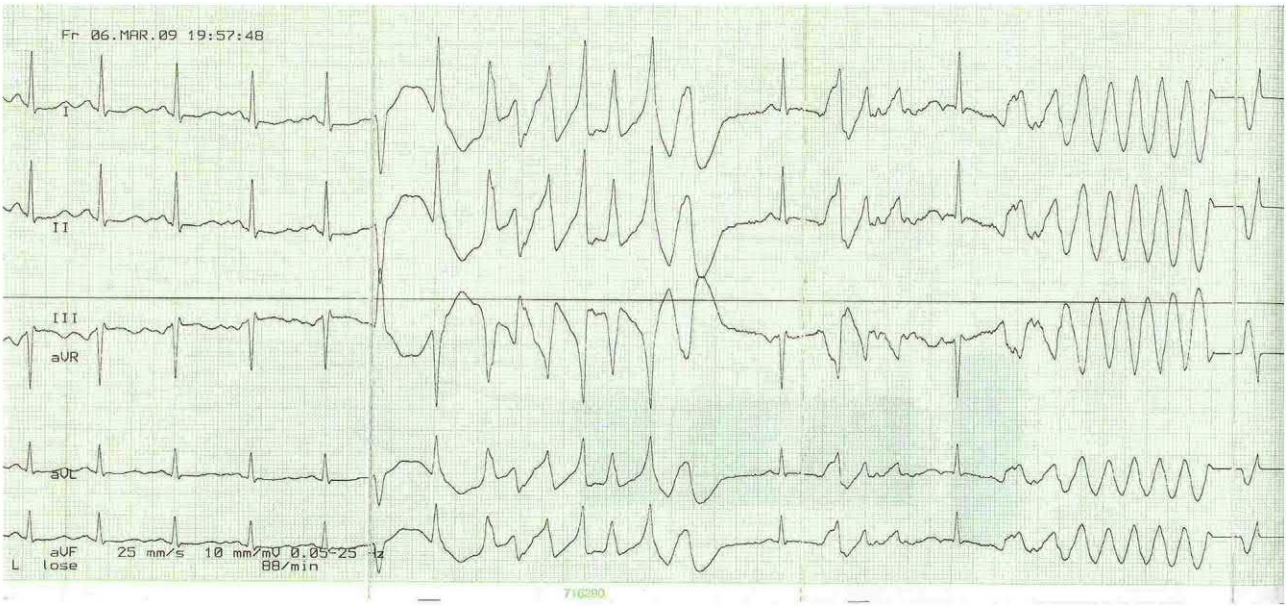

FIGURE 26.2 Examples of different pattern of ventricular tachycardias in one individual—electrocardiogram recorded in a 47-year-old female treated by plaquenil—QT interval prolonging drug—and with concomitant hypokalemia. In the left part of the tracing, the regular heart rate allows to differentiate markedly prolonged QT interval (QTc at least 540 ms). In the center, rather bizarre ventricular activities occur, while in the right part of the tracing, the nonsustained ventricular tachycardia is of almost monomorphic pattern.

scar-related, e.g., postmyocardial VT, the reentry circuit of TdP is functional and continuously changing as conduction blocks occur in areas where repolarization has not been finished yet due to pronounced repolarization heterogeneity.

Involvement of both focal and reentry mechanisms simultaneously was found in several studies while others observed perpetuation by focal activity only [13–18]. Recent computer modeling of human cardiac tissue suggested that the mechanism of TdP perpetuation depends on the degree of heterogeneity. If the degree of heterogeneity is large, focal activity alone can sustain a TdP, otherwise reentrant activity emerges [19]. Then the same group observed on an animal model that sustained episodes of TdP were all perpetuated by reentry, while spontaneously terminating TdP could be perpetuated either by purely focal activity or had mixed perpetuation, i.e., focal initiation followed by reentrant period terminated by another focal activity again. All the described mechanisms produced the typical "twisting of the points." If this is true also in humans remains to be confirmed [20].

Regional and transmural spatial heterogeneities in AP duration are important factors for reentry formation of TdP. However, there is only very limited data on sex differences in AP heterogeneities. In female rabbits, a transmural and base-to-apex gradients of $I_{Ca,L}$ were observed, while these were not found in rabbit males [21] (Fig. 26.3). Similar data for potassium repolarization currents are not available.

Clinical presentation of TdP

Fortunately, TdP is often self-terminating, but it may degenerate in ventricular fibrillation. In a set of 150 different episodes of TdP, the length of arrhythmia ranged from 3 beats up to 117 beats (16 ± 8 beats in average). The cycle length of 193–364 ms (with an average of 279 ± 47 ms) was observed. The TdP was often preceded by a bigeminy of premature ventricular beats forming the typical short-long-short triggering sequence [22] (Fig. 26.4). Due to its nonsustained nature, TdP usually leads to syncope. Seizures are often present because of which the event is not rarely misdiagnosed as an epilepsy. Noncoordinated muscular activity is present because the circulatory arrest is not complete during TdP and some of the QRS complexes are still followed by a contraction of the ventricles (Fig. 26.5). These reduced contractions are not able to keep consciousness, but they are sufficient for residual noncoordinated muscular activity.

Risk factors for TdP development

An increased risk for developing TdP is associated with QT interval prolongation; the other risk factors are congenital LQTS, heart failure, low level of potassium and magnesium, combination of QT interval prolonging drugs, and female sex. Fortunately, presence of a single risk factor does not lead to TdP, and typically multiple factor must be present simultaneously [23].

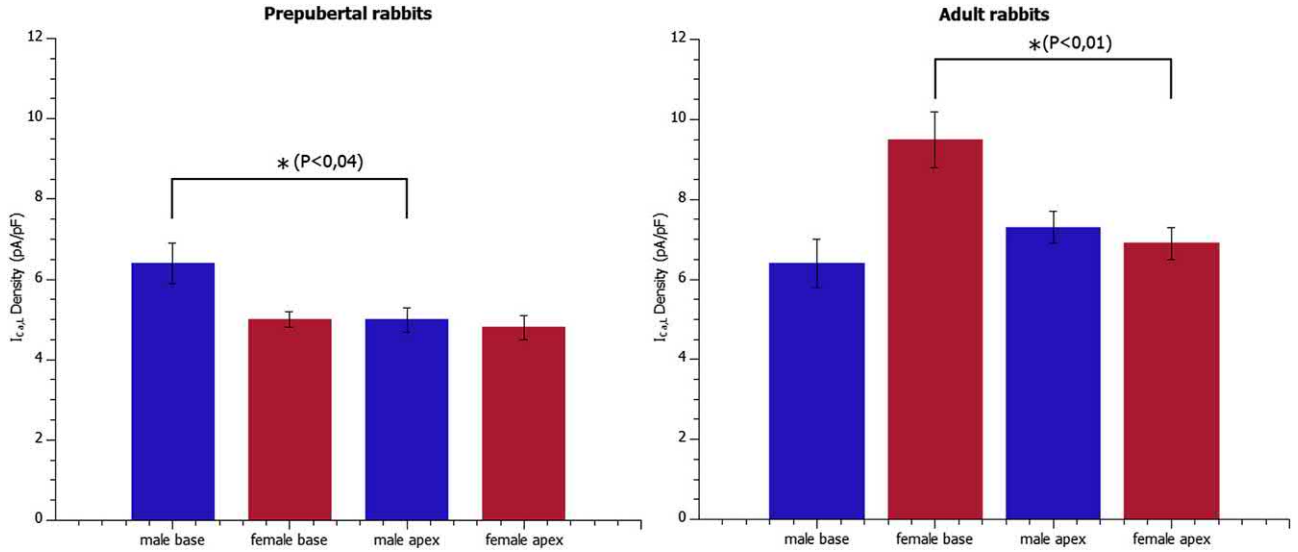

FIGURE 26.3 Apex–base distribution of $I_{Ca,L}$ densities in rabbits ventricles—in prepubertal male, epicardial cells form the base had significantly higher densities than those from the apex while the differences were not significant in prepubertal females. On the contrary, in adult rabbits, base-to-apex gradients of $I_{Ca,L}$ were observed in females, while these were not found in rabbit males. *Modified from Sims C, Reisenweber S, Viswanathan PC, Choi BR, Walker WH, Salama G. Sex, age, and regional differences in L-type calcium current are important determinants of arrhythmia phenotype in rabbit hearts with drug-induced long QT type 2. Circ Res 2008;102:e86–e100.*

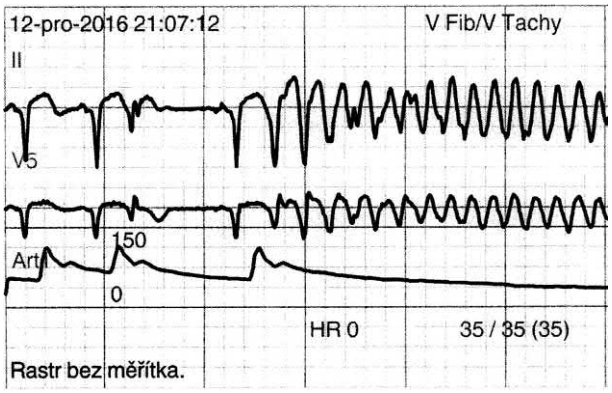

FIGURE 26.4 The typical trigger of TdP—the short-long-short sequence of sinus rhythm and premature ventricular beats.

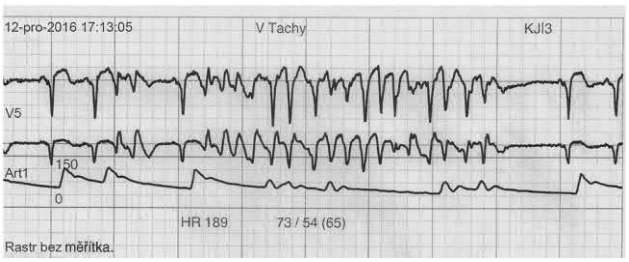

FIGURE 26.5 An episode of self-terminating TdP: ECG recordings in the upper two traces. The lowest line records blood pressure measured invasively through arterial line showing that the circulatory arrest is not complete during TdP and some of the QRS complexes are still followed by a contraction of the ventricles.

In a large metaanalysis assessing 332 cases of TdP, 70% of the affected individuals were females [24]. A recent study analyzed data from 22,214 patients (33% women) with 84 TdP events (56% women) [25]. The study confirmed that QT interval prolongation was associated with an increased risk for TdP. Interestingly, female sex was associated with an increased risk for TdP even after adjustment for confounding variables. The other independent predictors were age and congestive heart failure (Fig. 26.6). The affected individuals had also lower potassium levels, but no differences in magnesium were found. While this analysis included data from antiarrhythmic drug development programs, it is not fully clear if the results can be translated to other drugs.

Recently, an important observation concerning risk of TdP in patients with acquired atrioventricular block was published [26]. Of 250 (48% females) patients, 47 developed TdP. This subgroup consisted of 36 women, with only 11 men confirming that female sex was a strong risk factor. The main finding of this study was the fact that females developed TdP at QTc shorter than males (QTc 588 ± 75 ms vs. 638 ± 59 ms, $P = .035$ with Fridericia correction or QTc 588 ± 90 ms vs. 648 ± 62 ms for women vs. men with TdP, $P = .044$ with Framingham correction), although the severity of bradycardia at the time of TdP was similar for males and females (Fig. 26.7). Neither age was an independent risk factor. It is widely accepted that females are at higher risk of TdP due to their longer QT interval. The above described study shows that there must be other sex-specific factors that increase the risk of arrhythmias. In other words, the effect of sex goes beyond the AP duration. Editorial commentary to this study emphasized the reduced repolarization reserve in females as a possible explanation [27]. Nevertheless, again multiple risk factors (QT prolongation, female sex, and bradycardia) had to be present for the development of TdP.

Incidence

The incidence of drug-induced TdP is difficult to estimate. First, in the literature, in many cases, it is not easy to differentiate whether reported drug-induced LQT cases refer only to QT interval prolongation or also to TdP occurrence. Second, cases of TdP are often not correctly recognized. Third, the way of data collection is important—data based on spontaneous reporting are probably underestimating the problem. Fourth, definition of populations is often imprecise (e.g., number of inhabitants in a region in one study, number of patients admitted to a particular hospital in the other study), thus comparison of study results is difficult.

European reporting rates of TdP ranges from 0.11 in Italy to 12 in Sweden. If active surveillance approach is applied, estimates are considerably higher—a study in Southwest France carefully examining medical records (without requiring electrocardiographic evidence of QTc/TdP) came to the incidence of diagnosed nonfatal torsades as around 10.9 per million per year and women have a greater susceptibility to TdP in drug-induced LQTS than men (51% vs. 49%) [28]. Another study in the area of Berlin was based on documented QT interval prolongation together with at least one of the following clinical signs: evidence of TdP or successful cardiac resuscitation or syncope or severe dizziness. With this approach, the calculated annual crude incidence rate of TdP was 3.2 per million person years (0.0032‰/year). Again, incidence rates were lower in males (2.5 per million person years or 0.0025‰/year) compared to females (4.0 per million person years or 0.004‰/year) [29]. In a recent study in Leuven, electronic medical files of all the patients in the database were manually reviewed to identify cases of TdP and an incidence of 0.159‰ per year in a hospital population was found. Interestingly, number of TdP cases in males and females was equal in this study [30]. Comparison of the two abovementioned studies is difficult due to completely different populations, which were studied; moreover, inclusion criteria were bit different. The true incidence could be even higher since many cases of drug-induced LQTS may not survive until they reach hospital.

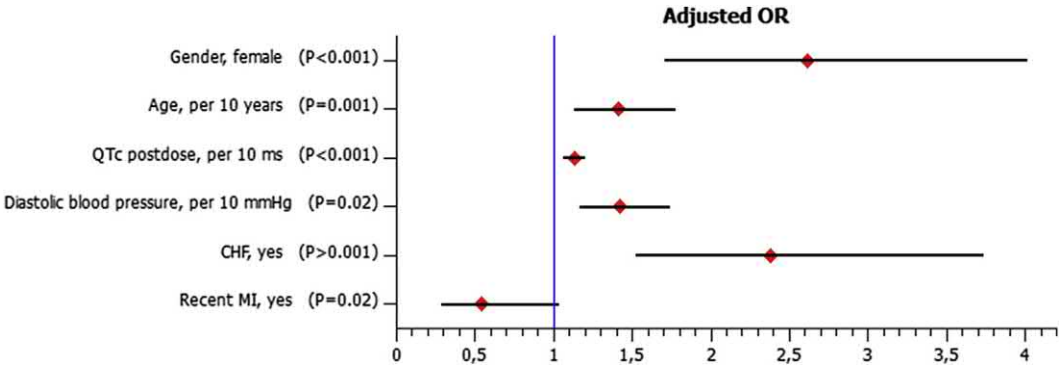

FIGURE 26.6 Risk factors for TdP development. Data from 22,214 patients (33% women) with 84 TdP events (56% women) from antiarrhythmic drug development programs. Female sex was associated with an increased risk for TdP even after adjustment for confounding variables. *Modified from Johannesen L, Garnett C, Luo M, Targum S, Sorensen JS, Nitin M. Quantitative understanding of QTc prolongation and gender as risk factors for torsade de pointes. Clin Pharmacol Ther 2018;103:304–309.*

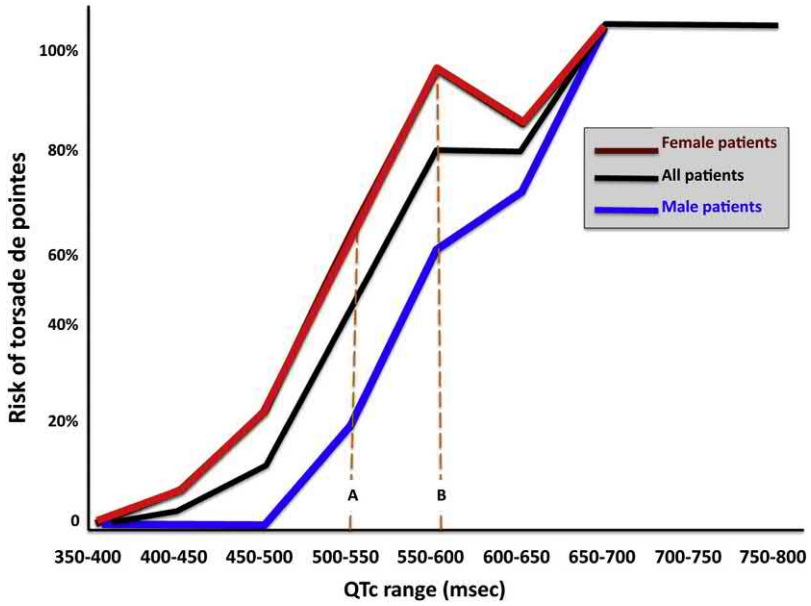

FIGURE 26.7 Risk of torsades de pointes (TdP) among males (*blue line*) and females (*red line*) and entire population with AV block (*black line*) as a function of QTc interval. As expected, the risk of TdP increases as QTc increases; however, female patients tend to develop TdP at shorter QTc intervals compared to males. For example, only 20% of males but >60% of females who had QTc between 500 and 550 ms had TdP (*dotted line* A). Similarly, all females with QTc 550–600 ms but only 60% of males with QTc in that range had TdP (*dotted line* B). *Reprinted from Chorin E, Hochstadt A, Viskin S, Rozovski U, Havakuk O, Baranchuk A, Enriquez A, Strasberg B, Guevara-Valdivia ME, Márquez MF, González-Pacheco H, Hasdemir C, Raphael R. Female gender as independent risk factor of torsades de pointes during acquired atrioventricular block. Heart Rhythm 2017;14:90–95. With permission from Elsevier.*

Conclusion

TdP is a specific polymorphic VT related to specific conditions. Mechanisms of its initiation and perpetuation are still not fully understood. Striking sex differences are present not only in mechanisms; its incidence is higher in women, with female sex being an independent risk factor.

Acknowledgment

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Part VIII

Training and sport

Chapter 27

Electrophysiological adaptations to endurance and strength training

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Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

Introduction

Women's participation in both competitive and recreational sport has traditionally been lower compared to men. Since the 1980s, women's participation in sports has progressively increased [1]. The lower participation of women may still be visible in leisure-time exercise training. Worldwide, women tend to be less physically active than men, but the magnitude of the difference between sexes varies between countries [2]. While the largest differences in favor of men may be due to cultural reasons and tradition, it can be anticipated that the gap will decrease in the future. This would be desirable, since the health benefits of regular exercise, especially for cardioprotection, are well known, and moderate levels of regular endurance and strength training are recommended for everyone [3]. However, most data on cardiac adaptations to training still come from men. The reasons for the lack of female data may be similar to those responsible for the lower sport participation of females. Furthermore, the menstrual cycle causes physiological fluctuations and provides an additional factor that needs to be controlled in a thorough study design.

At the top end of the physical training and performance curve are athletes. Athletes are a highly specialized group of individuals, and it is not clear whether cross-sectional findings on the physiological limits of cardiorespiratory performance and cardiac electrophysiology can be generalized to the average population, such as those who are just beginning an intensive exercise training program. This chapter will review evidence from both cross-sectional studies on athletes and longitudinal evidence from previously sedentary individuals who have begun a regular exercise training regimen. The chapter will begin by examining the physiological adaptations behind the altered ECG in athletes and then shortly describe the most common features of the ECG in athletes. The focus will be on the heterogeneity of the athletic population and the diversity of their training programs. The chapter will also address the challenging topic of dose-response of exercise training and adaptation. The principles of training adaptation will be highlighted throughout the chapter. The remainder of the chapter mainly focuses on the changes in heart rate and heart rate variability in different measurement situations, including submaximal and maximal exercise. Additional benefits of a long-term follow-up will also be reviewed, including monitoring the balance between training load and recovery (i.e., overtraining).

Physiological basis for divergent adaptations to exercise training

Training adaptation is a process where the repeated stress of exercise leads to altered structure and function of the human body. The desired training adaptations are those that lead to improvements in physical performance. Through adaptation, a well-designed training program improves sport-specific performance, i.e., a human's ability to perform a certain physical task. Different training stimuli result in different adaptations, in accordance with the training specificity principle [4]. For the sake of simplicity, exercise stimuli are often divided into endurance and strength stimuli, depending on whether cardiorespiratory or neuromuscular adaptations, respectively, are desired. In reality, sport disciplines and especially their training regimes include both cardiorespiratory and neuromuscular elements. A more continuous classification of sports is the proportion of maximal strength and cardiorespiratory fitness utilized during sports performance [5]. Top performance in weight lifting, for example, is largely determined by muscular strength, whereas long distance running requires a functional cardiorespiratory system to deliver, absorb, and utilize oxygen during exercise. The physiological limit of oxygen utilization during maximal exercise

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is termed maximal oxygen uptake (VO_2max), and it is a key concept of endurance exercise.

VO_2max is not the only determinant of endurance performance, but it is the most important measure of cardiorespiratory fitness, and it effectively differentiates endurance athletes from the normal population [6]. VO_2max provides a framework for many of the cardiac adaptations observed in endurance athletes. VO_2max is a product of central (i.e., cardiac) and peripheral (i.e., muscular) factors according to the Fick equation:

$$VO_2\text{max} = (\text{left ventricular (LV) end-diastolic volume} - \text{LV end-systolic volume}) * \text{heart rate} * \text{arteriovenous oxygen difference} \quad (27.1)$$

While peripheral adaptations and changes in microvasculature play an important part in the high VO_2max in athletes, high VO_2max is mainly a result of high cardiac output. Maximal heart rate does not increase but rather decreases somewhat in response to endurance training, and therefore, high VO_2max in athletes can be traced back to a large stroke volume (Fig. 27.1) [6,7]. Large stroke volume is the result of large ventricular size and enhanced ventricular function. A large part of the differences in VO_2max between fit and unfit individuals can be explained by cardiac size, especially left ventricular mass and ventricular end-diastolic volume [6,8]. Similarly, between men and women, the larger cardiac size in men contributes to their larger VO_2max compared to women. Central and peripheral factors together result in a sex difference in VO_2max of around 20%, which is similar in both untrained and trained young individuals [9].

Endurance training is characterized by a high total volume of hemodynamic load. The cardiac muscle is required to pump at a high rate for long periods. Strength training, on the other hand, includes exercises with high neuromuscular loads that can only be repeated a few times. Athletes participating in sports characterized by long-lasting training sessions such as cyclists and cross-country skiers tend to have considerably larger cardiac adaptations compared to those participating in high force but short duration events like weight lifting [10,11]. As a result, endurance athletes have larger cardiac cavity dimensions than strength athletes. Against the widely accepted Morganroth hypothesis on volume and pressure overload associated with endurance and strength exercise, respectively, a difference in the volume of hemodynamic

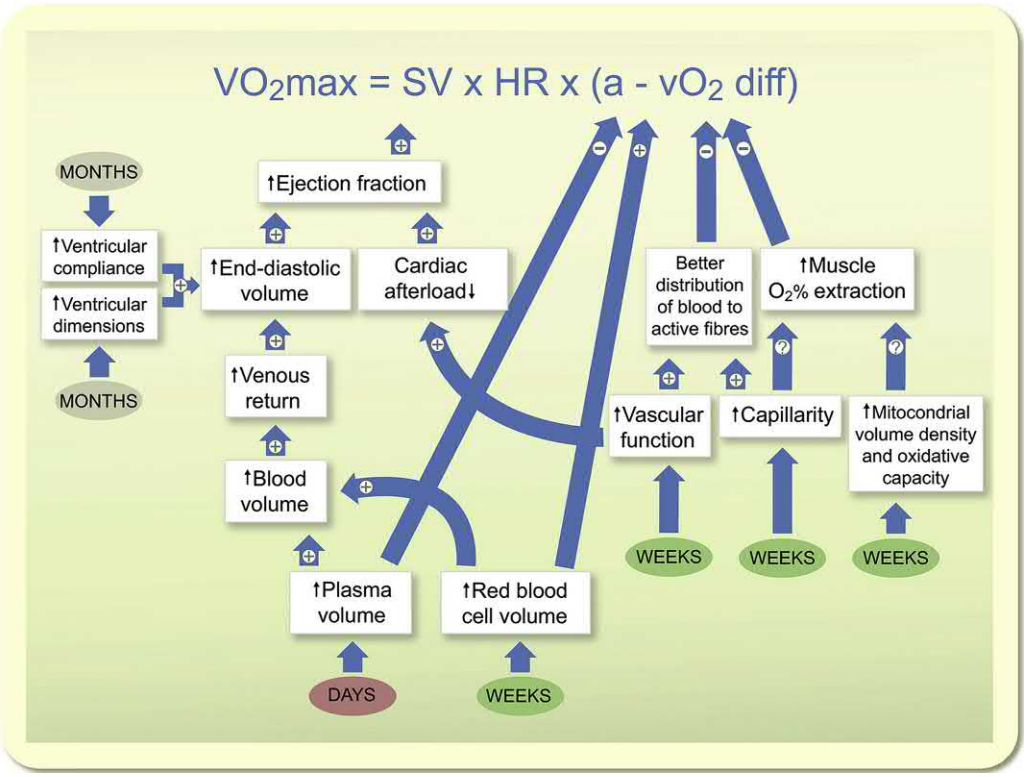

FIGURE 27.1 Summary and time course of the adaptations underlying high maximal oxygen uptake (VO_2max) of athletes. VO_2max is mainly determined by stroke volume (SV) and to a lesser extent by arteriovenous oxygen difference (a−v O_2 diff). Maximal heart rate (HR) decreases or does not change due to endurance training [7]. *Reprinted by permission from John Wiley and Sons: Acta Physiologica. Lundby C, Montero D, Joyner M. Biology of VO_2max: looking under the physiology lamp. © 2016.*

stimulus rather than training mode as such is a potential reason for the differences observed between the heart of an endurance and a strength trained athlete [12].

Sex differences in hormonal levels and body size have the potential to induce different hemodynamic responses to acute exercise. Even after correcting for differences in body size, women seem to have lower stroke volume than men during constant load exercise [13]. However, during incremental exercise, the relationship between VO_2 and cardiac output is constant in humans, which implies similar cardiovascular control in men and women during exercise [14]. Stroke volume increases throughout incremental exercise in both athletic men and women. A compliant heart and rapid diastolic filling enable stroke volume to increase in athletes, even at high heart rates during near maximal exercise, while in untrained men and women, stroke volume levels off at lower exercise intensities. Thus, the mechanisms behind the increase in stroke volume during exercise seem to be similar in men and women [15]. In male athletes, stroke volume during maximal exercise can be approximately 130−150 mL [6], whereas in untrained men and women, stroke volume is about 115 and 80 mL, respectively [9]. In endurance trained female athletes, maximal stroke volume can be 50% higher than in moderately trained females [16].

Normal ECG findings in an athlete

Training-induced changes in cardiac electrophysiology are common among athletes of various sports and levels. Differentiation between physiological and pathological changes may be difficult as the prevalence of underlying heart disease is low in this specialized population group [17,18]. Marked sinus bradycardia and prolongation of the PR interval are typical features of an athlete's ECG at rest, and they are often associated with high endurance performance and VO_2max. An average RR interval of as long as 2000 ms at rest (which is equivalent to a resting heart rate of 30 beats/min) and a PR interval of 400 ms have been reported in healthy highly trained endurance athletes. However, larger values than these are rare and may require further clinical investigation [19].

Due to cardiac remodeling induced by the hemodynamic load of endurance training, a large proportion of athletes have mildly to distinctly abnormal resting ECG according to standard clinical criteria [20]. Recently, a group of experts in sports cardiology created international recommendations for ECG interpretation especially for athletes [19]. In addition to sinus bradycardia, the most common ECG findings in athletes include incomplete right bundle branch block, isolated QRS voltage criterion for ventricular hypertrophy, early repolarization, first-degree atrioventricular block, and respiratory sinus arrhythmia, which seem to be more prevalent in male compared to female athletes [21,22]. The difference in the prevalence between sexes may be due to less substantial left ventricular hypertrophy in female compared to male athletes [11]. However, failing to scale cardiac dimensions with an appropriate measure of body size may exaggerate the differences between athletes and the normal population or between men and women [23]. The main limitation of the sex comparison is that data still mainly come from male athletes.

In this context, it is important to consider the definition of "athlete". In the literature, the term athlete may refer to both amateur and professional individuals who have been engaged in sports of various disciplines for varying amounts of time [18]. As pointed out earlier in this chapter, total hemodynamic load seems to determine the level of cardiac remodeling. A dose−response relationship exists between training stimulus and training adaptation, but defining an exact threshold for training volume that shifts an individual from the normal reference group to the athletic reference group remains a challenge. Along with providing recommendations for ECG interpretation for athletes, the sports cardiologists defined a threshold amount of training to be a minimum of 4 h per week [19]. A recent meta-analysis concluded that a decrease in resting heart rate seems to occur on average after 3 months of performing at least three weekly training sessions [24].

While the total duration or frequency of training per week is an effort toward standardizing training quantification in various sport disciplines, it is insufficient as it ignores an important component of exercise intensity and consideration of training history. An athlete's heart develops over a long period of time and under varying loads due to different types of training and competition. The reality is that there is no generally accepted method for training volume assessment across different training disciplines, which remains a major challenge in sport sciences. Furthermore, a genetic component may be a major determinant of electrophysiological adaptations. Therefore, rather than the volume of training, a resulting phenotype, VO_2max, has been suggested as a measure of athletic conditioning [18]. While VO_2max is not applicable in strength-trained athletes, it may be a useful standard for endurance athletes.

Dose−response relationship of training adaptations

Cross-sectional studies that compare athletes from different sports can rarely account for the actual features of their training, i.e., training volume and type of training. Training volume, i.e., dose, is a product of absolute exercise intensity, duration, and frequency of exercise bouts, and it is often defined by total energy expenditure induced by the

exercise [25]. Type of training refers to the physical component, which determines the main aim of the training session: endurance, strength, speed, or flexibility. These training design variables (intensity, duration, frequency, and type) vary within endurance and strength disciplines and even between individuals within a sport discipline. Athletic training is rarely purely for endurance or strength but includes components from the whole continuum of training types, intensities, and durations.

One year of progressive endurance training with an aim of completing a marathon has been shown to lead to some of the cardiac adaptations observed in endurance athletes in previously sedentary men and women [26,27]. For example, VO_2max increased from 40 to 47 mL/kg/min and resting heart rate decreased from 67 to 57 beats/min. At the end of the training period, both men and women were able to train near the typical level of an endurance athlete. However, a large part of the adaptations occurred during the first 3−6 months of training when the training volume was moderate. Further increases in training volume did not lead to equivalent adaptations, and the physiological outcomes fell far behind the level observed in endurance athletes. Longitudinal training studies typically report a decrease in resting heart rate of a few beats per minute while remaining in the normal range (>60 beats/min) [28,29], whereas resting heart rates reported in athletes can be as low as 30 beats/min [19]. A few studies have examined the extent to which selection bias in cross-sectional studies on athletes and genetic influence explain the difference between athletes and controls. Male and female twin pairs, discordant for leisure-time physical activity, had a difference of approximately 10 beats/min in their resting heart rate after a 36-year follow-up [30]. Genetic factors may explain both the baseline level of heart rate and training-induced changes through similar genetic components [31].

Sex differences in training adaptations are a challenging field of study, partly because it is difficult to standardize training volume. One of the principles of training prescription is that it needs to account for individual differences at baseline. Therefore, when comparing training adaptations between men and women, the baseline fitness level and training history need to be similar, not in absolute but in relative terms, taking the higher baseline fitness level of men into account. A comparable training protocol for men and women means that in absolute terms of training volume, women train less than men do. As the anticipated training adaptation occurs, the progression principle of training prescription necessitates that the training stimulus needs to be increased to match the increased level of training tolerance. In the long term, if there are differences in training adaptation between sexes and training volume is adjusted accordingly, different training progression will occur. Dose and response will thus go hand in hand.

Very different doses in terms of total training volume may also induce similar training adaptations. Sprint interval training is a training mode that is characterized by low duration and high intensity (at or above the intensity that corresponds to VO_2max), which together result in much lower training volume than conventional endurance training. Men and women increase their cardiorespiratory fitness similarly after 6 weeks of sprint training standardized by body mass [32]. The underlying electrophysiological mechanisms behind the cardiorespiratory adaptations are not well understood [33]. It is possible that peripheral mechanisms are more important than cardiac modulation when considering the improved VO_2max [34]. The shortest sprint intervals examined are only 20 s in duration, which is close to the duration of a single set of hypertrophic strength training. However, the higher hemodynamic load of sprint training still distinguishes it from the strength training stimulus.

Evidence of sex specificity in heart rate adaptations

According to a meta-analysis, women have a higher heart rate and lower total heart rate variability but higher high frequency power component of heart rate variability at rest compared to men [35]. As these results are not controlled for physical activity or fitness level, the lower participation in regular exercise training that has been reported in women may explain some of the sex differences [2]. In general, endurance training seems to decrease resting heart rate and increase heart rate variability. A cross-sectional study showed that the prevailing level of physical activity was independently associated with heart rate and heart rate variability in both men and women [36]. However, the dose−response relationship may be different in men and women. In another study, higher volume of moderate and vigorous physical training was associated with a lower resting heart rate and higher heart rate variability in men. In women, a similar association was only observed with regards to vigorous activity and resting heart rate [37].

Clear longitudinal evidence of different training adaptations does not exist between sexes. Similar training adaptations in resting heart rate have been reported after 20 weeks of standardized training [29]. Some studies may have unfortunately been underpowered to detect the potential sex effect or do not report results separately for men and women [38]. Short-lasting training interventions may also be a concern when investigating sex-specific adaptations. Differences in training adaptation may only become evident as the training continues for several months [39]. Therefore, training intervention studies shorter than 3 months may miss important differences between sexes in cardiac adaptations. But even with a long-term follow-up, longitudinal changes in cardiac electrophysiology may be

minor and difficult to detect if the athletes are already well-conditioned with a high baseline performance level. In a 1-year follow-up of elite endurance athletes, only the mean heart rate changed over time, decreasing simultaneously with increasing training load toward the competitive period. Heart rate and heart rate variability of male and female athletes changed similarly throughout the training season when the amount of training between sexes was comparable (Fig. 27.2) [40].

Strength training interventions that involve the whole body or large muscle groups and lead to marked improvements in muscular strength do not seem to alter resting heart rate or heart rate variability in young [41,42] or older men [43] or women [44]. Even 6 months of progressive strength training did not change heart rate or heart rate variability in previously untrained older women [45]. Some minimal overlap between endurance and strength training adaptations may occur in untrained individuals who may receive a sufficient cardiovascular stimulus from short bursts of muscular work. A recent meta-analysis summarized results from 181 articles and concluded that endurance training tends to decrease resting heart rate in both men and women, whereas the effects of strength training are minor, clinically negligible, and statistically significant in women only [24].

Training-induced bradycardia is widely believed to be a result of increased vagal activity at rest. High heart rate variability occurs in athletes in parallel with low heart rate, and heart rate variability is considered as an indirect measure of cardiac autonomic function. This has led to the conclusion that the large heart rate variability especially at the respiratory frequencies in athletes, i.e., high frequency power and the root mean square of successive RR interval differences (rMSSD), is a sign of high vagal activity [46]. More recently, it has been pointed out that the difference between athletes and untrained individuals increases after parasympathetic blockade and persists after complete autonomic blockade [47]. These findings suggest that sinus bradycardia is due to decreased intrinsic heart rate and modulations of the sinus node and conduction system along with autonomic adaptations. Heart rate and the magnitude of variability are associated, so a decrease in heart rate is expected to produce an increase in heart rate variability even without changes in vagal tone. To what extent heart rate variability depends on average heart rate remains uncertain [48].

The magnitude of training adaptations is partly genetically determined [31]. Some phenotypes, dependent or independent of sex, may also explain the individual differences in training adaptations. Interestingly, in the context of cardiac electrophysiology, a recent review article concluded that vagal activity may causally determine individual ability to exercise [49]. Support for this notion is provided by the finding that the amount of endurance training adaptation may partly be explained by the baseline level of heart rate variability [50]. Furthermore, scheduling training sessions based on the prevailing heart rate variability results in larger gains in endurance performance compared to similar predetermined training in men. In women, reducing the frequency of vigorous intensity exercises based on decreased heart rate variability led to similar adaptations than higher training frequency with fixed prescription [51]. However, few training interventions have been able to take the menstrual cycle into account

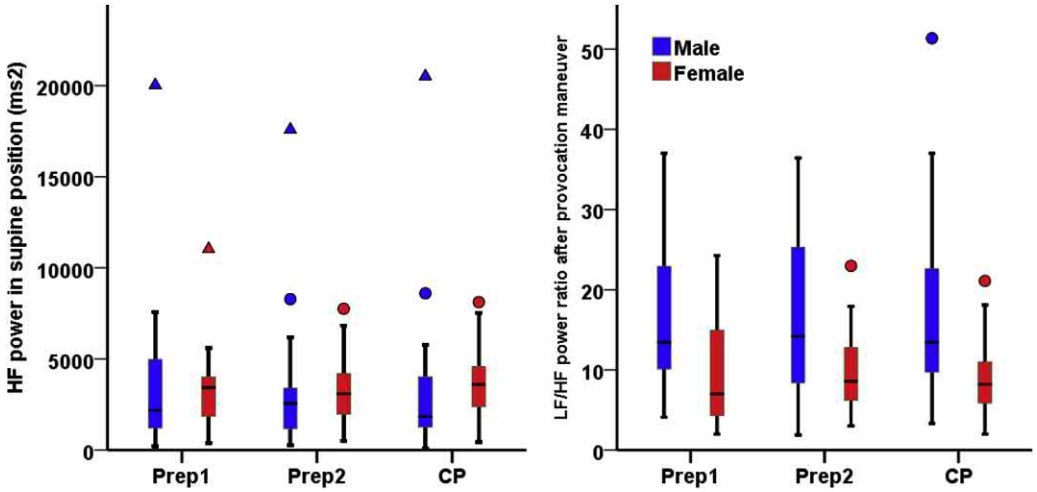

FIGURE 27.2 High-frequency (HF) power of heart rate variability was similar between sexes (left panel) but the low/high-frequency power ratio (LF/HF) after a provocative maneuver (orthostatic challenge) was significantly higher in male compared to female athletes during preparation period 1 (prep1) and competition period (CP) (right panel) [40]. *Adapted by permission from Springer Nature: European Journal of Applied Physiology. Schäfer D, Gjerdalen GF, Solberg EE, Khokhlova M, Badtieva V, Herzig D, et al. Sex differences in heart rate variability: a longitudinal study in international elite cross-country skiers. © 2015.*

when timing the training sessions. The function of the autonomic nervous system fluctuates during the menstrual cycle, potentially due to ovarian hormone levels, and is a potential confounder of sex differences [46].

Training effects observed during and after acute exercise

The acute effects of exercise on cardiac electrophysiology provide additional tools for the analysis of training effects, as exercise produces dynamic changes in autonomic activity. The onset of exercise increases sympathetic drive and reduces vagal tone. Vagal withdrawal during exercise makes some of the training-induced changes in resting ECG, such as sinus bradycardia and first-degree atrioventricular block, disappear [17]. While resting heart rate shows minor to moderate training effects in the normal population, submaximal heart rate at a standardized exercise intensity seems to change more both in relative and absolute terms. Regular and long-term endurance training also induces electrophysiological changes that are only observed at the onset, during, or after cessation of exercise, of which a few examples are provided here.

Of the heart rate values recorded during exercise, maximal or peak heart rate attained during a maximal graded exercise test is the most frequently used. It is an important reference point for measuring training intensity, since submaximal heart rate requires normalization to individual maximum. A recent study provided reference values for maximal heart rate for men and women at different ages [52]. The data show a small but significant difference between sexes in the age-related decline of maximal heart rate, and furthermore, it provides sex-specific prediction equations for the estimation of maximal heart rate. Especially in men, larger body mass index predicted lower peak heart rate, whereas in women, age was a more dominant predictor. The accuracy of the frequently referenced estimation of maximal heart rate based on a decline of one beat/minute per year of age has been questioned and should not be used as more accurate equations exist [53,54]. In response to training, maximal heart rate changes very little [29], and if anything, decreases in both men and women [39].

Submaximal exercise reveals some sex differences in cardiovascular function during acute exercise. The same relative workload brings about lower arteriovenous oxygen difference and lower stroke volume index (adjusted for body size) in women (Fig. 27.3). At the same time, submaximal heart rate was higher in women when corrected for cycling power output. This means that women and men may have different reliance on peripheral and central mechanisms during training when exercise intensity is standardized relative to maximal workload [13]. This difference could also be carried over to longitudinal training adaptations, but strong evidence for long-term sex differences is lacking. Heritability of the magnitude of training adaptation in submaximal heart rate is estimated to be approximately 20%−30% with no significant sex difference in the familial correlations [31]. Submaximal heart rate at the same absolute exercise intensity has been shown to decrease more in women than in men [29]. This may, however, be due to the higher relative intensity that the utilized intensity imposed on women as higher submaximal exercise intensity may yield a clearer training effect [43].

The cessation of exercise generates an immediate decrease in heart rate. The speed of heart rate recovery immediately after exercise is partly mediated by vagal reactivation [55]. Heart rate recovery is another important measure of autonomic function, and it is usually quantified as the difference between final (peak) heart rate at the cessation of exercise and the heart rate after one or 2 min of recovery [56]. While speed of heart rate recovery after maximal exercise may also reflect sympathetic withdrawal, it may be more tightly linked to parasympathetic reactivation after submaximal exercise [57]. Impairment of heart rate recovery 1 min ($\leq$12 beats/min) or 2 min ($<$22 beats/min) after the cessation of exercise is independently associated with mortality [56,58]. In a healthy sample of adults, slow heart rate recovery was more common in women, whereas the age-related decrease in heart rate recovery during a 20-year follow-up was larger in men [59].

Heart rate recovery after both submaximal and maximal exercise has been shown to reflect longitudinal changes in athletic performance [60]. It should be noted that relative exercise intensity and exercise protocol significantly affect the speed of heart rate recovery [60,61]. Therefore, for effective follow-up of heart rate recovery, the exercise intensity needs to be standardized. The faster heart rate recovery observed in men seems to be due to the higher cardiorespiratory fitness of males, as the sex difference is abolished when controlling for VO_2max [62] (Fig. 27.4). Although the effects of strength training on heart rate variability seem to be minor, there may be a significant increase in postexercise heart rate recovery in men [63].

Observations from long-term ambulatory recordings

A complicating feature of electrophysiological adaptations is that the level achieved with intensive training is not constant but fluctuates along with increasing and decreasing training load (Fig. 27.5) [64]. Therefore, it is important to know the exact phase of the training cycle as well as other life stressors, since these factors may have a

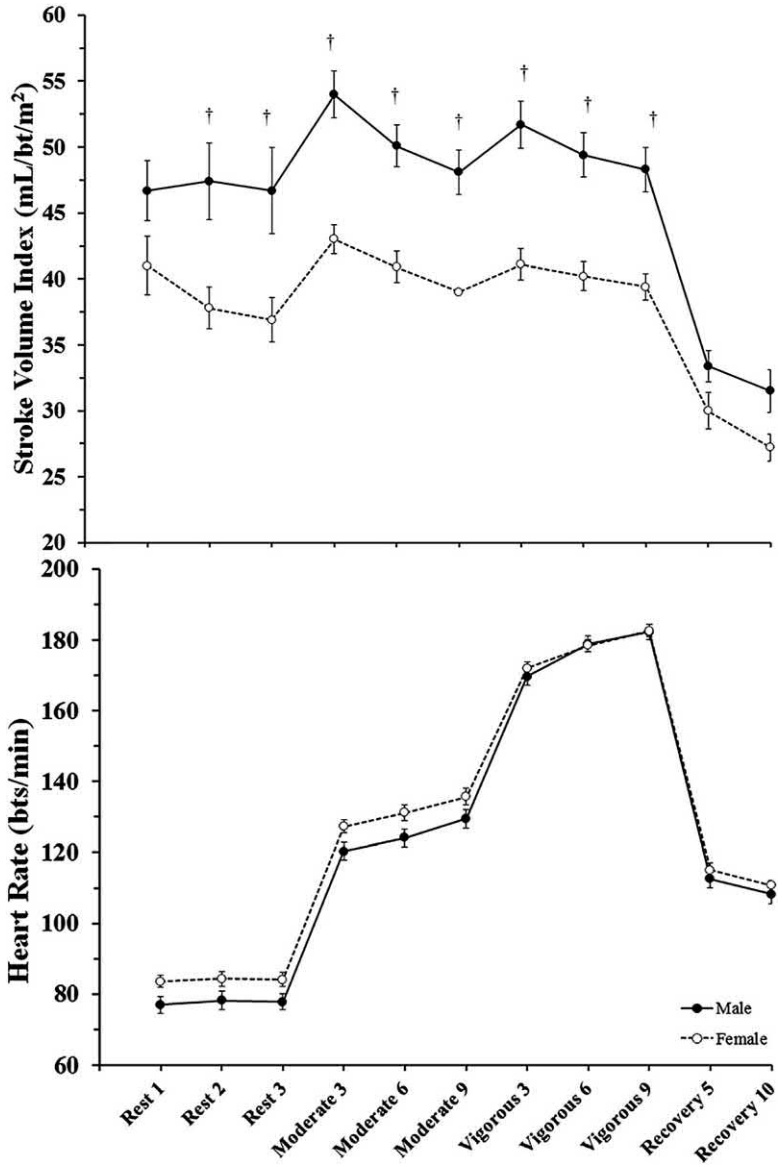

FIGURE 27.3 Stroke volume index at rest and during constant-load moderate (~40% peak workload) and vigorous (~70% peak workload) exercise was significantly higher (†, $P < .01$) in men. Submaximal heart rate was similar at the same relative loads but higher in women when corrected for cycling power output [13]. *Adapted from a figure by Wheatley et al. under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0), Wheatley CM, Snyder EM, Johnson BD, Olson TP. Sex differences in cardiovascular function during submaximal exercise in humans. © 2014.*

large effect on the results and interpretation. Temporary fatigue and a decrease in performance resulting from an intensified training period is part of a typical training cycle. However, increasing the volume and frequency of training can only lead to positive adaptations when the relationship between stress from the exercise stimulus and time to recover from it is in balance over time relative to individual training tolerance. If recovery is insufficient in the long term, physical performance is decreased rather than increased, due to accumulated fatigue. There is a subtle distinction between functional overreaching, which is a temporary decline in performance, and nonfunctional overreaching, and both of these are distinct from overtraining syndrome. By definition, it takes several weeks or months to come through overtraining syndrome. The main component of treatment is rest or significantly reduced training volume [65], which can be detrimental for athletic success.

Overtraining is common in both male and female athletes. However, the estimated prevalence of overtraining syndrome varies due to the lack of conclusive diagnostic tests and the required length of follow-up period to confirm

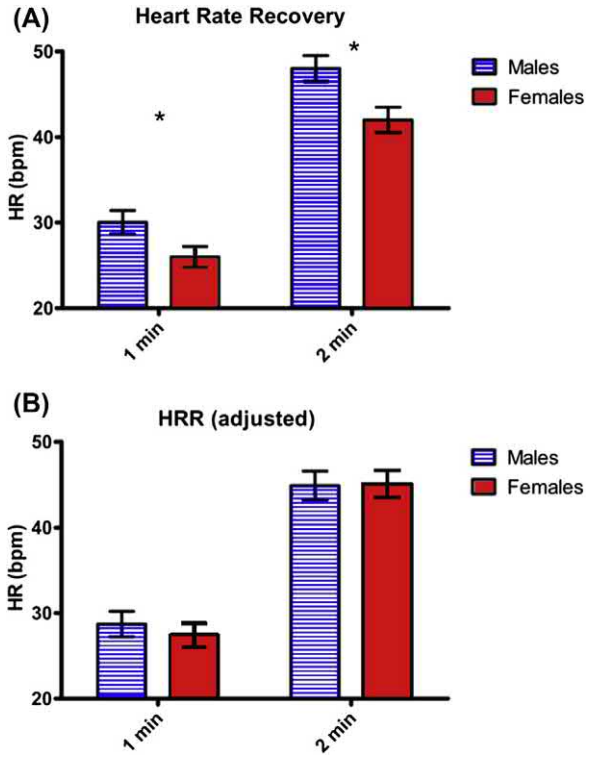

FIGURE 27.4 Statistically significant (*$P < .05$) sex differences in the absolute values of beats per minute (bpm) of heart rate recovery (HRR) are abolished after adjusting for VO_2max. HRR was measured 1 and 2 min after cessation of maximal exercise [62]. *Adapted from a figure by Kappus et al. under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0), Kappus RM, Ranadive SM, Yan H, Lane-Cordova AD, Cook MD, Sun P, et al. Sex differences in autonomic function following maximal exercise. © 2015.*

the diagnosis. One of the largest overtraining studies conducted to date, with almost 400 athletic participants, reported an estimated combined prevalence of nonfunctional overreaching and overtraining of approximately one-third in young English athletes with somewhat higher incidence in females (36%) compared to males (26%) [66]. Overtraining seems to be more common in athletes who have previously been diagnosed with overtraining syndrome [67]. Based on the varying diagnostic criteria and limited data available, it is difficult to determine conclusively whether female athletes are more prone to overtraining. Insufficient recovery is one possible explanation for blunted ventricular hypertrophy in females, which was shown to plateau after only a few months of training, whereas males continued to show ventricular hypertrophy for several months. Other possible explanations for blunted adaptations in females include hormonal differences and insufficient energy intake, as reflected by reduced body fat during intensive training phases [39].

Balancing on the thin line between functional and nonfunctional overreaching and preventing overtraining has become an important part of athletic conditioning. Ambulatory monitoring of heart rate or RR interval–derived heart rate variability metrics are popular means for long-term monitoring of training load and recovery. Alterations in training load are believed to cause notable changes in cardiac autonomic balance. Positive training adaptations are generally believed to increase and overreaching to decrease vagal-related indices and total heart rate variability [68]. For example, the standard deviation of RR intervals reportedly shows a bell-shaped relationship with the highest deviation occurring at modest training loads, which may indicate some level of overtraining at the highest training loads [27]. However, conclusive scientific evidence for the associations between overtraining syndrome and cardiac electrophysiology is lacking due to several methodological limitations. Next, the limitations and potential solutions will be shortly addressed.

Firstly, there is no generally accepted method to quantify sympatho-vagal balance noninvasively from heart rate variability measures. Long-term monitoring of a rolling weekly average of a repeatable vagal-related index (such as rMSSD) in the morning upon waking has been recommended [68]. Secondly, the amplitude of changes in heart

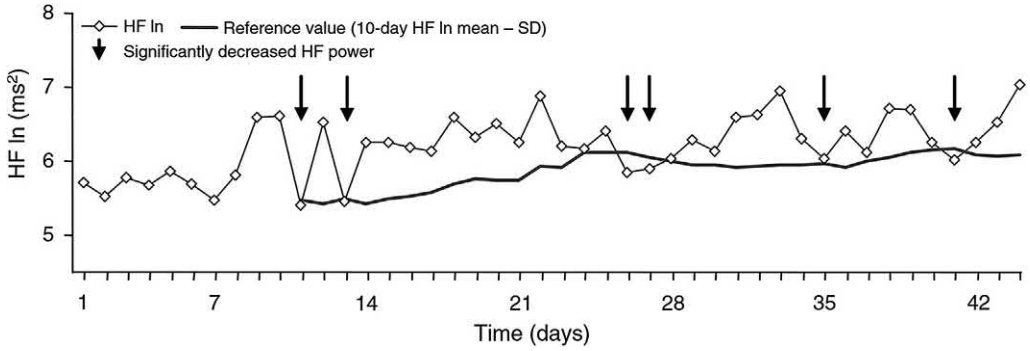

FIGURE 27.5 Daily high-frequency (HF) power of heart rate variability fluctuates due to alterations in training load and other factors that affect parasympathetic modulation. Thus, a 10-day average of natural logarithm (ln) of HF power minus standard deviation (SD) has been calculated to see the long-term trend [64]. *Adapted by permission from Springer Nature: European Journal of Applied Physiology. Kiviniemi AM, Hautala AJ, Kinnunen H, Tulppo MP. Endurance training guided individually by daily heart rate variability measurements. © 2018.*

rate and heart rate variability is small to moderate in relation to daily fluctuation and thus difficult to detect [69]. The direction of change may also be individual and depend on physical fitness, training history, and genetics [68]. Thirdly, overtraining syndrome develops over a long time, and the process includes periods of both functional and nonfunctional overreaching. Thus, long-term monitoring and detailed information about training cycle and other life stressors are required to interpret heart rate data. Lastly, some of the cardiac autonomic changes observed in a fatigued state after an intensive training period (confirmed by decreased physical performance) are similar to those of positive training adaptations: a decrease in maximal heart rate, decrease in submaximal heart rate, and an increase in heart rate recovery [69,70].

Whether there are sex-specific autonomic responses to overtraining is not clear due to the limited data available. Iwasaki et al. observed an increase in the average RR interval length at rest with increasing training load in both men and women who were previously untrained [27]. Kiviniemi et al. showed an altered relationship between RR interval length and its variability (computed as high-frequency power) in overtrained male and female athletes and a change in the relationship after 6 months of recovery [71]. The drop in heart rate variability observed after an intensive training session may take longer to normalize in women compared to men [51]. Fatigue and recovery are, however, complex physiological phenomena, and slower recovery of one parameter cannot be considered as evidence of slower recovery overall in women. For example, women seem to have higher resistance to muscular fatigue than men [72]. Since overtraining syndrome is characterized by various physiological and psychological symptoms, detection and prevention may also require a multidisciplinary approach [73].

Summary

Sex differences in training adaptations are a complicated field of study, and many longitudinal studies have failed to show any significant differences between males and females. However, there are some indications based on long-term follow-ups and prolonged training interventions that over time, women may exhibit blunted cardiorespiratory adaptations to endurance training. This may partly explain the higher prevalence of abnormal ECG or "athlete's heart" in male compared to female athletes. The current recommendations for health-enhancing physical activity are not different for men and women [3]. Examining how males and females respond to similar exercise training may, in the future, help to determine whether men and women require sex-specific training guidelines to be able to achieve their maximal or optimal level of adaptation.

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Chapter 28

Exercise-based cardiac rehabilitation

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Content of cardiac rehabilitation

Cardiac rehabilitation (CR) is designed to optimize secondary prevention of coronary heart disease (CHD) targeting for the safe return to daily life and normal physical activities. The main objectives of CR and secondary cardiovascular disease (CVD) prevention are to reduce recurrent events and premature disability in patients with CHD and increase the chances of longer life expectancy [1]. Multidisciplinary CR approach focuses on patient education, nutritional counseling, modification of the risk factors, psychosocial management, individually tailored exercise training, and the overall well-being of patients [2–5]. Core components of CR programs and follow-up measures are presented in Fig. 28.1 [4].

CR programs are defined as multifactorial and comprehensive, with physical activity counseling and exercise training as key components in all rehabilitation and preventive interventions. This is justified because many of the risk factor improvements occurring in CR can be mediated through exercise training programs [6]. Although CR programs very often focus on exercise training only, a crucial point to consider is a CR program based more on the individual's needs and goals aiming at the improvement of the quality of life in terms of smoking cessation, healthy eating, weight management, increase and maintenance of both daily habitual physical activity and exercise training and their volume and intensity, decreased blood pressure, lipids and glucose management to optimize cardiovascular risk reduction, and reduced disability. The scope of contemporary CR could be shifted from exercise interventions only to more comprehensive and individually customized secondary prevention programs with education, psychological support, and stress management [4,7].

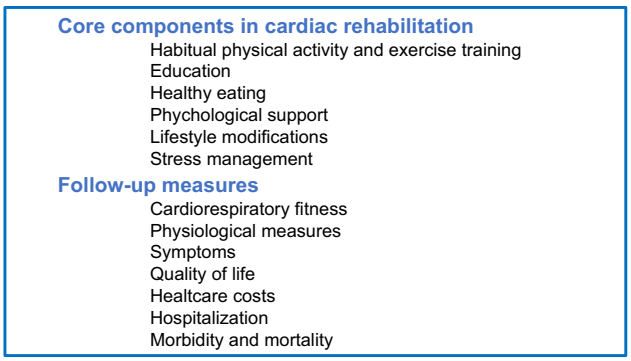

FIGURE 28.1 Key elements of cardiac rehabilitation programs and follow-up measures. Modified *from Laukkanen JA. Cardiac rehabilitation: why is it an underused therapy?. Eur Heart J 2015;36(24):1500–1501.*

Exercise-based cardiac rehabilitation

Benefits of exercise-based cardiac rehabilitation

International guidelines endorse the use of exercise-based CR programs [2,8,9]. Both modalities of training and endurance and resistance training are highlighted in guidelines of CR in addition to daily habitual physical activity. Exercise-based CR in low-risk patients after myocardial infarction (MI), percutaneous coronary intervention, or heart failure (HF) has reduced hospital admissions and improved health-related quality of life compared with usual care alone in many western societies [10]. Exercise-based CR programs have also reduced overall premature mortality by about 20% and cardiac deaths by about 30% in comparison with usual care of cardiac patients [11–14]. Furthermore, the benefits of CR are observed after a long-term follow-up (5 years). The composite outcome of hospitalizations for cardiovascular causes and cardiovascular mortality was lower in CR group compared with no-CR group (18% vs. 30%) and by lower hospitalizations for cardiovascular causes (15% vs. 27%) [15].

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The findings of Cochrane update (2016) confirmed the previous Cochrane findings (2011) showing important benefits of exercise-based CR that include a reduction in the risk of death from a cardiovascular cause and hospital admission and improvements in health-related quality of life compared with no-exercise control patients [16]. Cochrane review included 63 trials which randomized 14,486 patients with CHD at least 6-month follow-up. The patients were predominantly post-MI and post-revascularization patients with the mean age of patients in different studies ranging from 48 to 71 years. Women accounted for fewer than 15% of the patients recruited. It is also worth mentioning that the population studied in this review still consists largely of lower risk individuals following MI or revascularization.

In the Cochrane analysis (2019) with HF patients ($n = 5783$) with a median of 6-month follow-up, exercise-based CR appeared to have no impact on mortality in the short term (<12-month follow-up), but some evidence showed CR to reduce the risk of all-cause hospital admissions and may reduce HF-specific hospital admissions in the short term (up to 12 months) [17]. Many patients in studies included to analysis had HF with reduced (<45%) ejection fraction, and women, older individuals, and those with preserved (≥45%) ejection fraction were underrepresented. Furthermore, recent metaanalysis suggests that exercise-based CR rehabilitation improves health-related quality of life and exercise capacity in patients with HF, irrespective of patient characteristics [18].

Populations around the world are rapidly aging, which will increase demand for health care services. Advanced age is also associated with a higher prevalence of CHD as well as increased morbidity and mortality. Cardiac patients with advanced age (>75 years) benefit from exercise-based CR similarly compared with younger patients, although elderly very often have more severe cardiac disease and other comorbidities [8,19,20]. Cardiorespiratory fitness has been shown to improve at average of 7% after 4-week exercise intervention [21]. There is no markable increased risk of adverse cardiac events for elderly cardiac patients associated with exercise-based CR [22].

The evidence also suggests that CR is cost-effective, especially with exercise as a component [23–27]. However, research is needed to determine the most cost-effective design of CR and country-specific data to support decision-making of health care systems may be needed.

Exercise-based cardiac rehabilitation prescription

Endurance training is prescribed in terms of intensity, duration, frequency, and progression, including, for example, walking, jogging, cycling, and water-based exercise activities. The intensity of endurance training can range from 40% to 80% of baseline exercise capacity, depending on the fitness of an individual, as well as training goals. Lower intensity may be used in sedentary adults and those who are older or frail. However, for most adults, training intensities of 55%–80% of the baseline exercise capacity are well-tolerated and safe. Ideal training goals are to exercise ≥5 days a week for 30–60 min, depending on the training intensity. High-intensity interval training (HIIT) has also been suggested to be part of endurance training prescription in addition to continuous training modes [28–30]. It is structured as intense exercise periods alternating with relatively lower intensity recovery periods [6,9]. However, although HIIT appears to be usable exercise modality for cardiac patients, certain contraindications to HIIT, e.g., unstable angina pectoris or uncompensated HF, need to be considered before implemented to exercise prescription [31].

Resistance exercise training involving muscle activities that use low- or moderate-repetition movements against resistance is a primary component of a comprehensive exercise training program for cardiac patients, in addition to endurance training. Training programs include 1–3 sets of 8–10 major muscle group exercises performed 2–3 days weekly. Intensity of training is prescribed relative to the one repetition maximum (1RM), which is the highest load an individual can perform for a specific exercise. A repetition range of 10–15 at the intensity of about 40%–60% of 1RM is recommended for cardiac patients [6,9]. Guideline prescription for exercise training is presented in Fig. 28.2 [9].

Exercise-based CR should be started soon after hospital discharge. A typical feature in the current clinical practice is that the time for in-hospital stay period has tended to be shorter than previously and cardiac patients will be discharged relatively soon after an acute event and coronary interventions. This may cause some challenges into implementation of rehabilitation during the in-hospital phase. Usually CR should consist of three phases: inpatient, outpatient, and independent maintenance. Although no constant timeline of the phases exists, outpatient CR may be started within 14 days after the event in patients with uncomplicated MI, percutaneous coronary intervention (patients with normal or mildly reduced left ventricular ejection fraction), within 4 weeks in patients with minimally invasive open-heart surgery, and after 6 weeks in patients with heart surgery involving sternotomy [32].

Safety of exercise-based cardiac rehabilitation

The safety of CR is well established, with a low risk of major cardiovascular complications. The risk of a cardiac event during vigorous exercise training in cardiac patients have been estimated from supervised CR programs indicating about 1 cardiac arrest for every 115,000 patient-hours of CR and 1 death for every 750,000 patient-hours of participation [9]. In addition, the risk of a cardiovascular event has been shown to be low after both HIIT and

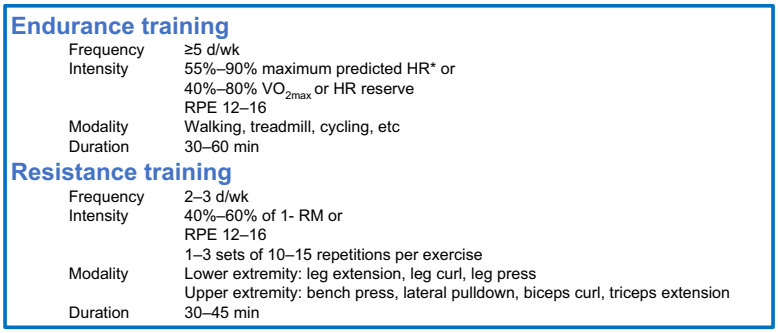

FIGURE 28.2 General guidelines for endurance and resistance training for coronary heart disease patients. *HR indicates heart rate; maximum predicted HR=(220−age); VO_{2max}, maximal oxygen consumption; RPE, rating of perceived exertion; and 1-RM, highest load an individual can perform for a specific exercise. *The HR range recommendation assumes that the individual is not taking β-adrenergic−blocking medications. Modified from Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013;128(8):873−934.*

moderate-intensity exercise continuous endurance exercise in a CR setting [33]. Similarly, HIIT early after an episode of HF decompensation and a CHD event has been documented to be safe and effective in improving exercise tolerance and health-related quality of life in selected patients after achievement of clinical stability [34]. Specific recommendations for risk stratification of exercise testing and training are provided in international guidelines [6,9,35].

Cardiac rehabilitation referral, enrollment, and adherence

Despite its proven benefits, CR referral and participation rates have been very low. Systematic CR remains underutilized among patients with CHD mainly because of referral problems, poor enrollment and support, and various local reasons because of limited resources. CR should be easily attainable in most cardiac patient cases. Although maintaining long-term adherence to CR may be challenging, efforts aimed at improving long-term adherence and motivation to CR programs should be monitored and assessed, ideally using large nationwide registers. The average referral rate has been reported to range from 19% to 34% in the United States [36] and an average of 30%−50% in Europe [5,37]. Interestingly, over 1500 CR programs across Europe have been recognized, existing in approximately 90% of countries, but there is only one spot for every seven patients in need [38]. To monitor the indications for CR, to assess the methods used and quality of care and the clinical outcome, the implementation of multinational CR databases seems a desirable tool.

Current evidence suggests that center-based CR is the most appropriate therapeutic approach for patients with CHD. On the other hand, home-based CR and tele-based CR may save time, effort, and resources and may be preferred by some patients. Systematic reviews indicate that tele-based CR improves cardiovascular risk factors and health-related quality of life, decreases the risk of cardiac events, and is cost-effective [39]. Despite the lack of long-term follow-up data regarding tele-based CR, emerging evidence indicates that improvements in telemonitoring technology have enhanced patient exercise capacity compared with regular center-based training. The importance of comprehensive CR should be strengthened because of the continuous changes in the population, including aging cardiac patients with multiple comorbidities.

The reasons for underuse are well-documented and include patient-, provider-, and healthcare system-level factors. According to Euroaspire IV survey, older age, women, low socioeconomic status, enrollment with percutaneous coronary intervention, unstable angina, previous history of CHD, HF, hypertension, or dysglycemia has been reported as features of patients those less likely will be advised to participate a CR program. In addition, patients who attend a CR have lower anxiety and depression scores and better medication adherence as well [5].

In the previous Cochrane analysis (2019), in patients with MI, with angina, coronary artery bypass graft surgery or percutaneous coronary intervention, or with HF who were eligible for CR (n = 5299, males 64%), assessed interventions where the aim was to increase patient enrollment in adherence to and completion of CR. The results showed that strategies to increase enrollment were effective, particularly those that targeted healthcare providers, training nurses, or allied healthcare providers to intervene face to face. Interventions to increase adherence to programs and to increase completion were effective, but it remained unclear which specific strategies were implemented. For older patients, it was suggested that peer support or postdischarge visits may improve enrollment, and group sessions promoting self-regulation skills may increase completion [40].

In women, there were insufficient data according to Cochrane analysis to find out whether women-tailored programs were associated with increased utilization, but motivating women was found to be a key factor [40]. Despite the higher mortality and complication risk after an acute coronary syndrome, women are less frequently enrolled in exercise-based CR and if enrolled show a lower adherence [41–43]. Witvrouwen et al. reported a perspective on how to improve referral, enrollment, adherence, and outcome to exercise-based CR in women (Fig. 28.3). The strategies with structured approaches to inform the referring physician as well as the patient and offering more flexible individually tailored or tele/smartphone-based programs while addressing the socio-economic and psychological needs of the patients were shown to be effective to improve the admission, adherence, and outcome of exercise-based CR in women [44].

Finally, evidence highly suggests the promotion of CR programs to be implemented as an integral part of disease management for cardiac patients. According to calculations, the increase in CR participation from 20% to 70% would save 25,000 lives and prevent 180,000 hospitalizations annually in the United States [36].

Mechanisms for cardioprotection in exercise-based cardiac rehabilitation

Potential cardioprotective effects of increased daily habitual physical activity, structured exercise, and/or improved cardiorespiratory and musculoskeletal fitness have been widely documented in the literature. Several large-scale epidemiological studies have reported strong, inverse, and graded independent associations of cardiorespiratory fitness with the risk of future cardiac events [46]. Cardiorespiratory fitness, an index of habitual physical activity, integrates human body function under demanding physiological states and reflects an individual's functional capacity. Cardiorespiratory fitness is related to the ability to transport oxygen from the lung to the mitochondria to perform physical exercise. Left ventricular stroke volume, maximal heart rate, and arteriovenous oxygen difference at exercise have determined cardiorespiratory fitness level among cardiac patients. Beneficial effects of exercise and improved fitness include improvements in multiple risk factors together with antiatherogenic, antiinflammatory, antiischemic, antithrombotic, and antiarrhythmic effects [9,47,48]. Physical activity exerts cardioprotective effects via (i) improvement in cardiovascular risk factors such as blood pressure, biomarkers of insulin resistance, lipid, glucose, and natriuretic peptides; (ii) its antiinflammatory actions, by reduction in levels of inflammatory markers such as interleukins and C-reactive protein; (iii) regulation of white adipose tissue mass and adipokine expression; (iv) improvement in endothelial function which ultimately slows the atherosclerotic cascade; and (v) vagal control of heart rate and regulation of cardiac autonomic function.

Good adherence to CR may be also related to successful medical and other therapies in cardiac patients. It is

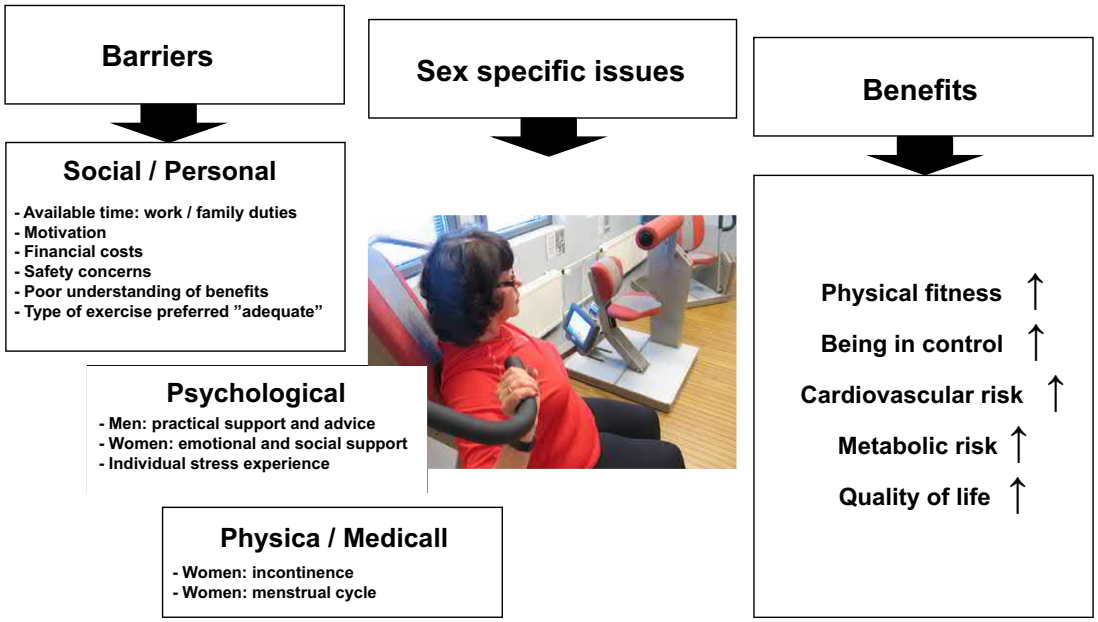

FIGURE 28.3 Barriers and benefits for exercise-based cardiac rehabilitation. Barriers may be shared or different between men and women, but benefits are shared. *Modified from Witvrouwen I, Van Craenenbroeck EM, Abreu A, Moholdt T, Krankel N. Exercise training in women with cardiovascular disease: Differential response and barriers - review and perspective. Eur J Prev Cardiol 2019;19:2047487319838221*[Epub ahead of print]*; Neubeck L, Freedman SB, Clark AM, Briffa T, Bauman A, Redfern J. Participating in cardiac rehabilitation: a systematic review and meta-synthesis of qualitative data. Eur J Prev Cardiol 2012;19(3):494–503.*

well-documented that optimal medical therapy with favorable lifestyle change including physical activity reduces cardiovascular outcomes. These findings support current clinical practice guidelines that recommend control of multiple risk factors to optimize secondary prevention [49]. Among subjects at high genetic risk for heart disease, a favorable lifestyle—no smoking, no obesity, regular physical activity, and a healthy diet—was associated with one-half the relative risk of incident coronary events associated with an unfavorable lifestyle [50]. The greater the number of risk factors in control, the higher the probability of survival in patients with CHD. More effective strategies are needed to achieve comprehensive risk factor control, including healthy behaviors with regular physical activity.

Electrophysiology in exercise-based cardiac rehabilitation

Exercise programs have been shown to improve cardiac autonomic function mainly expressed as increased heart rate variability (HRV) indexes [51–55] or increased heart rate recovery [56,57] in cardiac patients. Similar improvements after exercise-based CR have been also observed as baroreceptor sensitivity (BRS) in patients with MI [52,58]. In HF patients, exercise training focused interventions have improved autonomic function expressed as increased HRV, increased BRS, or decreased muscle sympathetic nerve activity [59–62] (Fig. 28.4). Similar benefits and reduced arrhythmias have been shown in congestive HF patients [60,63–65].

Effects of exercise-based CR on electrocardiographic markers such as of ventricular repolarization have not been extensively studied. QT dispersion, which is defined as the difference between the maximum and minimum QT interval of the 12-lead ECG, has been shown to be accompanied by favorable changes in metabolic parameters after a 4-week CR program in post-MI patients and discussed that this decrease was mediated by autonomic factors based on the favorable changes also observed in HRV [66]. Similarly, patients with preserved left ventricular ejection fraction after MI showed that exercise training induced significant reductions in corrected QT interval duration and in QT and JT dispersion [67]. Guiraud et al. reported exercise-induced improvements in QT dispersion in metabolic syndrome patients with and without CHD without improvement in metabolic parameters or functional capacity [68]. However, due to serious difficulties using concept of QT dispersion as a noninvasive estimate of repolarization abnormalities [69], the above-mentioned observations may be more likely related to the changes in T wave morphology rather than QT dispersion concept per se.

The effects of exercise-based CR were studied on T wave alternans (TWA), a measure of repolarization abnormality, in 24-hour ambulatory ECG recordings in patients with stable CHD without and with type 2 diabetes mellitus. Ambulatory ECGs were recorded before and after a 2-year training period. The results showed that exercise program reduced TWA both with and without type 2 diabetes [70] (Fig. 28.5).

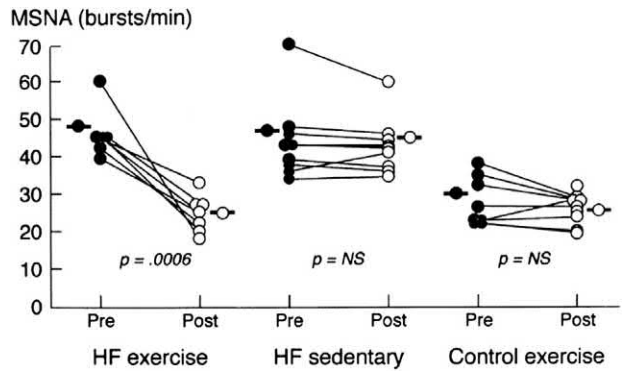

FIGURE 28.4 Muscle sympathetic nerve activity (MSNA) quantified as bursts/min. Postexercise training MSNA levels compared with pretraining MSNA levels in heart failure (HF) patients are uniformly and markedly reduced and are no longer higher than normal controls; MSNA remained unchanged in the HF sedentary group and the normal control exercise group. *Reprinted from Roveda F, Middlekauff HR, Rondon MU, Reis SF, Souza M, Nastari L, et al. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. J Am Coll Cardiol 2003;42(5):854–860 with the permission of the publisher.*

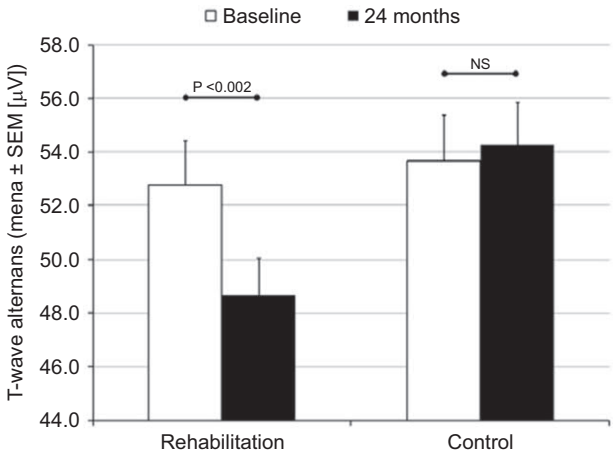

FIGURE 28.5 Significant reduction in T wave alternans (TWA) levels by exercise-based cardiac rehabilitation. In the combined group of coronary artery disease patients without and with diabetes mellitus, rehabilitation (n = 65) reduced TWA from baseline compared with 24-month follow-up. The control group (n = 65) showed no improvement in TWA. *Reprinted from Kentta T, Tulppo MP, Nearing BD, Karjalainen JJ, Hautala AJ, Kiviniemi AM, et al. Effects of exercise rehabilitation on cardiac electrical instability assessed by T-wave alternans during ambulatory electrocardiogram monitoring in coronary artery disease patients without and with diabetes mellitus. Am J Cardiol 2014;114(6):832–837 with the permission of the publisher.*

Several mechanisms have been postulated to underpin the protective effects of physical activity and good fitness on cardiac arrhythmias, and these include both physiological and metabolic processes, such as beneficial modulation of CVD risk factors, regulation of cardiac autonomic function and vagal control of heart rate, reduction in inflammation and improvement in endothelial function, blood pressure, and lipid levels. Many of the positive changes after exercise-based CR in electrophysiological markers have been associated to physical activity and physical fitness. As an example, in cardiac patients with type 2 diabetes, reduced postexercise heart rate recovery compared with the cardiac patients without diabetes was reported, and that this was more closely related to reduced physical activity, low exercise capacity, and obesity than to the duration or metabolic features of type 2 diabetes, including glucose control or its microvascular or macrovascular complications. Finally, there were no significant differences in heart rate recovery between groups after adjustment for physical activity, exercise capacity, and obesity [71].

Sex-specific features of exercise-based cardiac rehabilitation

According to electrocardiographic and electrophysiological indexes, women have a longer corrected QT interval and a shorter sinus node recovery time compared with men. Furthermore, drug-induced torsades de pointes is more common in women, and sudden cardiac death and atrial fibrillation are less common in women [72].

Despite above-mentioned differences and several other sex-related differences in the cardiovascular system [44,72], women, including older women as well, benefit from comprehensive CR as much as men [73,74]. It has been emphasized that woman patients are more likely to be older, hypertensive diabetes and hypercholesterolemia diagnosed, obese and suffering HF, as well as lower exercise and functional capacity compared with men and may therefore need more careful risk evaluation before CR implementation. Older age in women may have more likely various exercise-limiting comorbidities such as arthritis, osteoporosis, and urinary incontinence. In addition, women have shown to score lower in health-related quality of life, and they are more likely to be diagnosed with depressive disorders and higher scores of anxiety at the recruitment of CR [8].

To summarize, the physiological and clinical benefits of exercise-based CR are widely established, but there is limited evidence on possible sex differences in training response. Based on current data, CR should be strongly recommended for both the sexes. In patients with CVD, exercise-based CR elicits favorable effects on the cardiac function, endothelium and skeletal muscle resulting to an improvement of quality of life, cardiorespiratory and musculoskeletal fitness, and left ventricular ejection fraction, resulting in reduced morbidity and mortality [44].

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Chapter 29

Arrhythmias due to athletic training

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Introduction

The associated benefits of regular exercise on the cardiovascular system are well-established [1].

Regular physical activity lowers the risk of cardiovascular disease and all-cause mortality by offering protection from type II diabetes mellitus, obesity, hypertension, and dyslipidemia [2–5]. This wealth of evidence has provided us with insight into the lower range of the dose–response relationship between exercise and cardiac morbidity; and support recommendations of 150 min of moderate-intensity, or 75 min of vigorous intensity exercise per week [6]. Most athletes engage in exercise doses which greatly exceed these recommendations, and several perform up to 20 times the current recommendations. This population provides researchers with a greater opportunity to evaluate the upper range of the dose–response relationship between exercise and cardiovascular health, which is poorly understood.

For the purpose of this chapter, an athlete is defined as an individual who engages in regular physical training and participates in official sports competition with an emphasis on excellence and achievement [7]. Rarely, an athlete will fall victim to exercise-associated sudden cardiac death (SCD). Exercise has traditionally been perceived as the "trigger" for ventricular arrhythmia (VA) in susceptible athletes that harbor quiescent cardiac disease. Emerging data over the last two decades suggest that exercise may serve as an independent cause of adverse outcomes by promoting a change in the myocardial substrate in a previously normal heart. The majority of these studies have focused on the identification of arrhythmias which originate from the atria or right ventricle (RV). This has led to the theory of an existing U-shaped relationship between exercise and cardiac morbidity (Fig. 29.1) [8]. The paradox of exercise promoting potential harm may be perceived as barrier against the modern epidemic in lifestyle-related morbidity and therefore warrants careful evaluation [9]. This chapter seeks to review the epidemiology of exercise-induced cardiac arrhythmias with a particular focus on existing sex-related differences. The pathophysiological mechanisms and clinical implications of these arrhythmias will also be considered.

The athlete's heart

Exercise-induced cardiac remodeling

The metabolic demands of skeletal muscle during exercise are met through increased cardiac output and oxygen uptake. Sustained elevation of cardiac pressures and volume loads associated with regular exercise promotes a series of electrical, structural, and functional cardiac adaptations (Fig. 29.2). The magnitude of these physiological changes, which collectively form the phenotype of the "athlete's heart," is influenced by several factors including age, body size, ethnicity, sporting discipline, and sex [10]. Occasionally, features of exercise-induced cardiac remodeling overlap with morphologically mild phenotypes of cardiac conditions associated with exercise-induced SCD and create a diagnostic challenge for physicians given the potential clinical, psychosocial, and economic consequences of an erroneous diagnosis.

Early studies of the athlete's heart focused solely on male athletes who have historically dominated the landscape of elite sport. In more recent times, mothers reaching the pinnacle of their sport have challenged the historical concept that regular intense physical activity promotes harm to the reproductive system. As a result, the number of female athletes has risen exponentially in the past three decades, with the International Olympic Committee expecting women to participate in equal numbers as men for the first time at the Olympic Games in Tokyo 2020 (Fig. 29.3). The increasing number of female athletes in this modern era of sport provides researchers with a greater opportunity to evaluate sex-specific differences in the phenotype of the athlete's heart.

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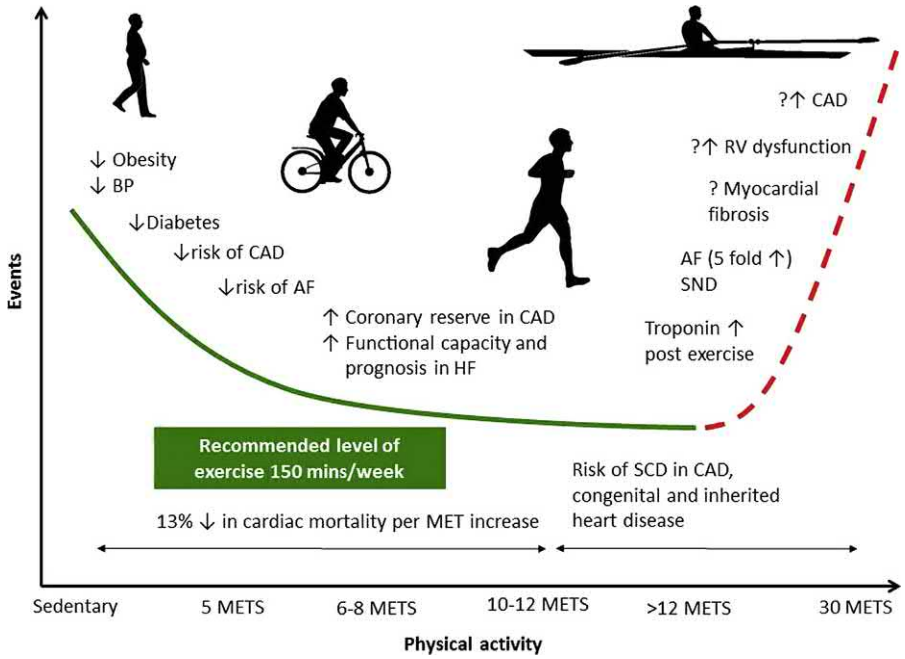

FIGURE 29.1 The U-shaped curve describing the dose–response relationship between exercise and cardiac morbidity. *AF*, atrial fibrillation; *BP*, blood pressure; *RV*, right ventricular; *SND*, sinus node dysfunction [8].

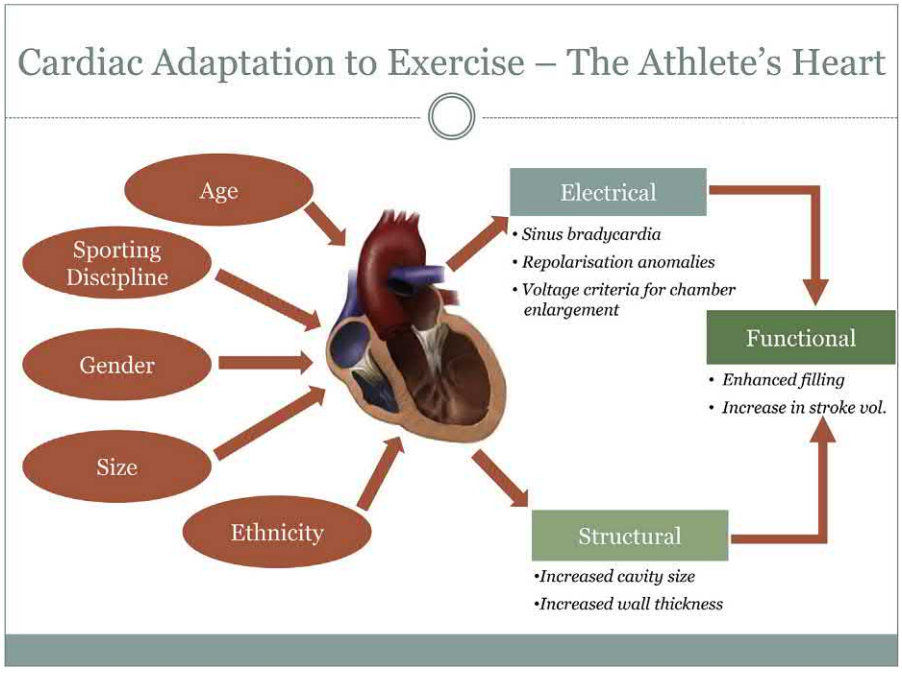

FIGURE 29.2 Determinants of physiological adaption in the athlete's heart [11].

Structural adaptation appears qualitatively similar between athletes in terms of sex, although female athletes exhibit smaller absolute values in cardiac dimensions compared with male counterparts [10,13,14]. The most plausible explanation for these differences is that women have lower circulating androgens and thus have a lower lean body mass and a lower capacity to perform vigorous exercise compared with their male counterparts. These differences are reflected in the fact that female athletes have a lower peak oxygen consumption compared with male athletes [15].

Irrespective of sex, the left ventricle (LV) of an athlete appears 10%–15% thicker and 10% larger than sedentary controls [16,17]. Almost half of a cohort of 1309 Olympic athletes (29% female) were identified with LV cavity dimensions which exceeded normal limits (left ventricular

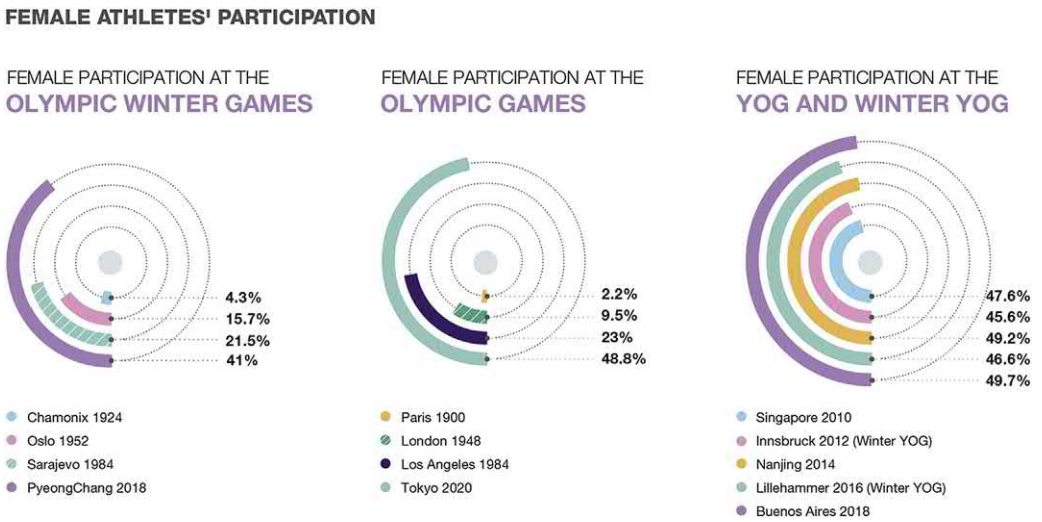

FIGURE 29.3 Women's participation in the Olympic Winter, Olympic Summer, and Youth Olympic Games (YOG) [12].

end-diastolic diameter > 54 mm). Marked LV dimensions of >60 mm overlap with dilated cardiomyopathy and were identified in 14% of male athletes and <1% of women [18]. As with sex, sporting discipline is also an important determinant of LV size and athletes participating in sports with a high dynamic modality (endurance) such as cycling and rowing show the greatest cardiac dimensions [18]. Cavity enlargement is not confined to the LV, however. A study of 543 athletes revealed that 61% of male and 46% of female athletes demonstrated RV cavity dimensions which met minor criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC) [19]. An LV wall thickness of >12 mm raises suspicion of hypertrophic cardiomyopathy (HCM) and is present in 2% of white male and 18% of black male athletes [20,21]. Irrespective of ethnicity, this finding is most unusual in female athletes [13]. Indeed, cardiac remodeling in females consists primarily of eccentric rather than concentric left ventricular hypertrophy [22].

The athlete's electrocardiogram

The changes associated with the athlete's electrocardiogram (ECG) reflect increased cardiac dimensions and vagotonia. Recognized physiological variants include sinus bradycardia, atrioventricular (AV) block (first-degree and Mobitz Type 1), junctional rhythm, voltage criteria for left or right ventricular hypertrophy, partial right bundle branch block, and the early repolarization pattern. The prevalence of these variants, excluding junctional rhythm and AV block [23], is observed less frequently in female athletes [17,24–28], suggesting that sex is an important determinant of ECG patterns in athletes, although the mechanisms which underpin these differences remain unclear.

Anterior T wave inversion (ATWI) is prevalent in 2.3% of young athletes (aged 16–35 years) and is more common in females and athletes. ATWI extending beyond V2 is rare, particularly in men, and warrants further evaluation [29]. T wave inversion in the inferior and/or leads has a relatively high positive predictive value for detecting an underlying cardiomyopathy and is a recommendation for further investigation, irrespective of sex [29–31]. In contrast, females exhibit greater QT intervals compared with males, which is recognized in the guidelines for ECG interpretation in athletes (Fig. 29.4) [32].

Arrhythmias in athletes

Atrial fibrillation

Atrial fibrillation (AF) is recognized as the commonest clinical arrhythmia in the developed world and is associated with an increased risk of stroke, heart failure, and mortality. The prevalence of AF in the general population of Europe continues to rise and is expected to double by the year 2060 [33]. Prevalence increases with age, affecting 0.5% < 40 years, 5% aged > 65 years, and approximately 9% > 80 years [34–36]. The main determinants of AF are increasing age, structural heart disease, and hypertension, although these are absent in 10%–15% of individuals, often labeled with "lone AF." Recent studies have challenged this term by attributing factors including obesity, obstructive sleep apnea (OSA), genetic predisposition, and endurance exercise.

It is well established that exercise mitigates established risk factors of AF including obesity, OSA, and hypertension. Indeed, low- to moderate-intensity exercise has been shown to not only prevent AF onset [37–39] but also

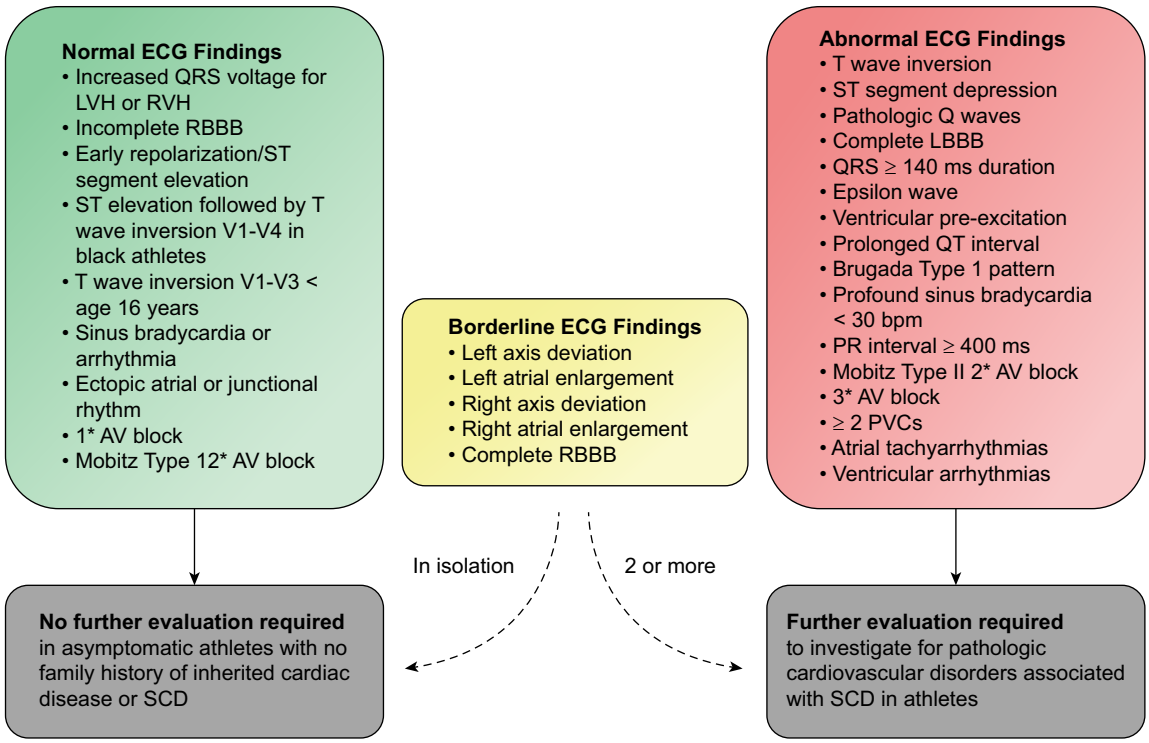

FIGURE 29.4 The 2017 international Consensus standards for electrocardiogram interpretation in athletes. *AV*, atrioventricular block; *LBBB*, left bundle branch block; *LVH*, left ventricular hypertrophy; *PVC*, premature ventricular contraction; *RBBB*, right bundle branch block; *RVH*, right ventricular hypertrophy; *SCD*, sudden cardiac death [32].

reduce the associated symptom burden, morbidity, and mortality in affected individuals [40,41]. A more recent body of evidence has emerged which supports a link between AF and long-term endurance exercise. This "exercise paradox" was first proposed at the turn of the millennium in small case−control and retrospective cohort studies [42,43]. The outcome of larger epidemiological studies and metaanalyses has subsequently demonstrated that the frequency of AF is 2−10 times greater in athletes engaged in long-term endurance exercise (e.g., marathon running, cross-country skiing, cycling) versus sedentary controls [42,44−51]. This weight of data supports the theory that the dose−response relationship between exercise and risk of AF follows a J-shaped pattern [46].

Researchers have made efforts to simplify the dose−response relationship by defining a threshold of exercise exposure which confers risk of AF, with estimates ranging between 1500 and 2000 lifetime training hours [43,52,53]. The wide variation in reported risk and exercise thresholds for AF is driven by study design factors, including collection methods (self-reporting, AF clinics, and retrospective review of health records), inconsistent definitions of what constitutes an "endurance athlete," selection bias associated with case−control and observational cohort studies, variations in the subjects age, training, and sporting discipline.

A significant caveat to this research is that these studies are largely derived from male cohorts and until recently it has been unclear whether the same J-curved pattern applies to female athletes. A recent metaanalysis of 650,000 individuals from 22 studies suggests that the relationship between exercise and AF may in fact be sex-specific. A pooled analysis of data from 150,000 women demonstrated that moderate-intensity exercise was associated with an 8.7% lower risk of AF, which increased further to 28% in those participating in high-intensity exercise. The dose−response relationship in men followed the same J-curved pattern described in previous studies (Fig. 29.5) [46]. In contrast, a cohort of 20,000 men and women were followed for an average 20 years in Norway [54]. Physical activity was assessed prospectively at intermittent periods and linked to hospital records which identified cases of AF. Moderate-intensity exercise was associated with a significantly reduced risk of AF over the 20-year follow-up period in both sexes. The risk of AF increased with high-intensity exercise in both sexes, although statistical significance was only demonstrated in male athletes. Inconsistent observations in female athletes have led investigators to believe that moderate-intensity exercise is protective for both sexes, whereas long-term high-intensity exercise is associated with sex-specific differences [44,48,54−59].

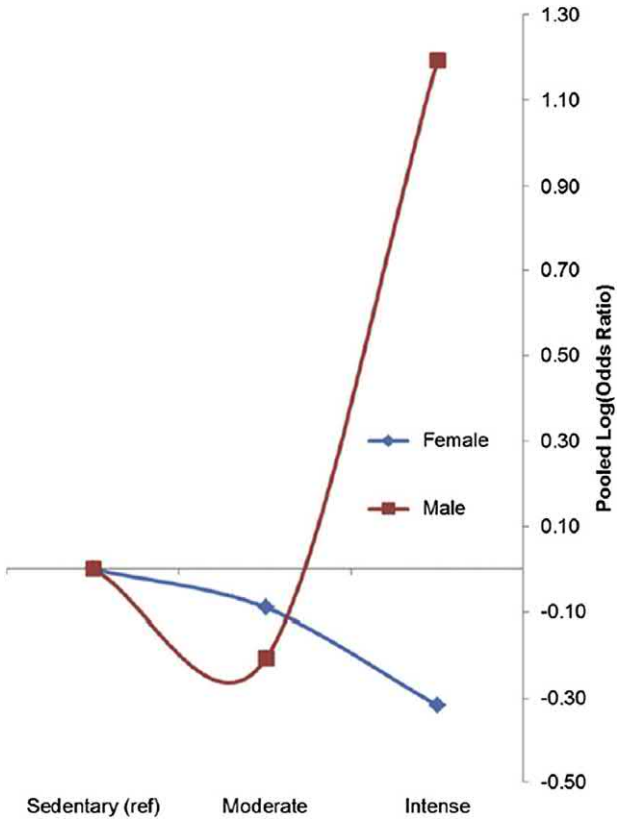

FIGURE 29.5 Association between level of physical activity and risk of atrial fibrillation in men and women [46].

The pathophysiological mechanisms which promote the development of AF in athletes are poorly understood. Proposed mechanisms are largely derived from animal models, small studies involving cardiac biopsy [60], and factors extrapolated from the general population which include atrial enlargement, atrial fibrosis, cardiac inflammation, pulmonary vein ectopy, genetic susceptibility, sympathetic tone, performance-enhancing drugs, and electrical remodeling of the sinoatrial node (Fig. 29.6) [61–65]. Sex-specific differences including endocrine factors and the inability to exercise as vigorously may explain why the J-curved pattern does not appear to apply to female athletes, although, to date, there remains insufficient evidence to reliably predict which athletes are at risk of exercise-induced AF [66].

Sinus node dysfunction

The most compelling evidence for exercise-induced sinus node dysfunction (SND) originates from a longitudinal study of 62 former professional male cyclists [67]. The control group consisted of 62 male golfers matched for age, weight, hypertension, and cardiac medication. The former endurance athletes demonstrated more frequent sinus bradycardia, SND, and pacemaker implantation for bradyarrhythmias relative to the control group. A higher than expected incidence of bradyarrhythmias was similarly reported in a 12-year follow-up study of 20 male marathon runners, with 10% (n = 2) of athletes requiring implantation of a permanent pacemaker [68]. Heightened vagal tone is normally attributed as the cause for exercise-induced bradyarrhythmias, although autonomic pharmacological blockade has revealed lower intrinsic heart rates in athletes compared with sedentary controls [69]. Experimental data in animal models have since suggested that training-induced bradycardia is a result of intrinsic remodeling of the sinoatrial node through downregulation of HCN4 and Tbx3 in pacemaker governing ion channel cells [70]. Currently, there are insufficient data to evaluate for sex patterns of exercise-induced SND. Our understanding of the epidemiology, pathophysiology, and clinical implications of such bradyarrhythmias warrants further investigation in larger longitudinal studies.

Ventricular arrhythmias in athletes

There are few studies examining the prevalence of VAs in athletes which are confined to male athletes. These studies have revealed conflicting results probably because of the small sample and the heterogeneous athlete cohort. One study of a 134 healthy middle-aged athletes (median age 45-year-old) showed that approximately 7% of male athletes revealed > 100 ventricular premature beats on a 24 h ECG and this prevalence is not dissimilar to age-matched controls [71]. Another study of 106 lifelong male endurance athletes with a mean age of 55.1 years old and 54 controls showed that almost 10% athletes had short runs of nonsustained ventricular tachycardia (NSVT) compared with none of the controls [72]. The cause and significance of NSVT in older athletes is unknown; however, it is possible that altered autonomic responses and adverse cardiac remodeling may be contributing factors.

Sudden cardiac death

Epidemiology of sudden cardiac death

The SCD of an athlete is generally attributed to VA arising from quiescent cardiac disease. The commonest cause of SCD in master (aged >35 years) athletes is atherosclerotic coronary artery disease (CAD), whereas inherited cardiac conditions such as cardiomyopathies and channelopathies predominate in young athletes (aged < 35 years). With an estimated incidence of 1:50,000 [73], SCD in young athletes is fortunately rare, although clear sex differences exist, with males reported to be at 2–10-fold risk compared with female counterparts in competitive sport [74–76] and as high as 20-fold risk in recreational sport [75]. The most common autopsy finding in young athletes is a structurally

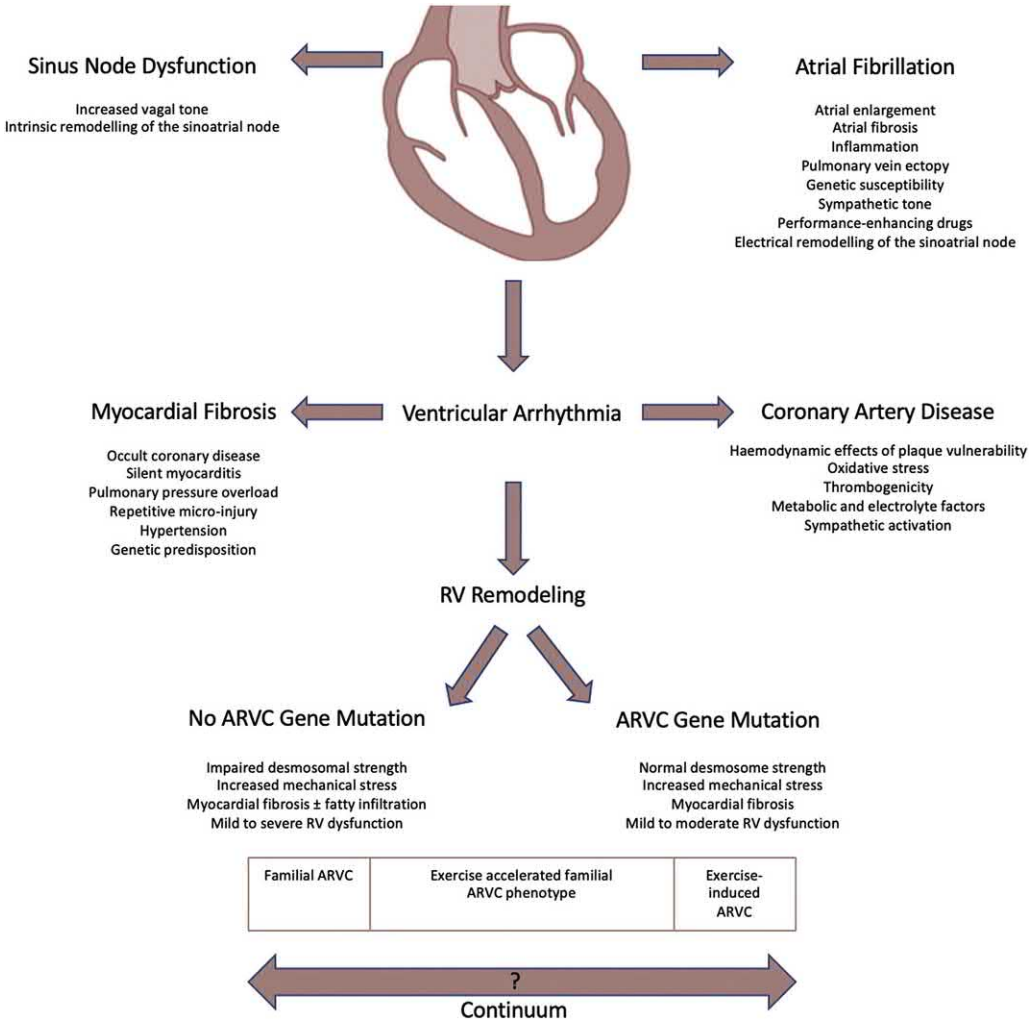

FIGURE 29.6 Proposed pathophysiologic mechanisms of exercised-induced cardiac arrhythmias in the endurance athletes.

normal heart which is referred to as sudden arrhythmic death syndrome or SADS [77,78]. SADS is attributed to inherited channelopathies including congenital long QT syndrome, catecholaminergic polymorphic tachycardia, and Brugada syndrome and thus requires comprehensive familial evaluation. Identification of individuals with such conditions has become an important focus of the medical community when we consider that the majority of responsible diseases can be detected during life, and acceptable risk-modifying strategies are available which include lifestyle advice, pharmacological therapy, and implantable cardioverter defibrillators.

Why are male athletes at greater risk of sudden cardiac death?

The higher reported prevalence of SCD in male athletes was previously attributed to the comparatively smaller number of females participating in competitive sports. The modern era of sport, however, has seen a significantly higher proportion of female athletes engaging in competitive sports without a paralleled increase of SCD incidence. This has challenged researchers to reconsider alternative theories to explain why female athletes appear at lower risk.

Women demonstrate longer QT intervals than men, which appear to evolve shortly after puberty, supporting the theory that sex hormones regulate cardiac repolarization which may lead to electrical instability and VAs [79,80].

Men demonstrate a higher phenotype prevalence of familial cardiomyopathies including ARVC and HCM [81,82], with the former being strongly linked to exercise and SCD [76,83]. Cardiac myocytes contain estrogenic and androgenic receptors which modulate the expression of specific cardiac genes and regulate the function of sarcomeric proteins. Estrogens inhibit myocardial hypertrophy whereas dihydrotestosterone promotes hypertrophy. These opposing effects may account, in part, for the higher prevalence of phenotypic expression for cardiac conditions such as HCM, which are associated with SCD [84,85].

Men are often perceived as poorer reporters of warning symptoms, which would ordinarily trigger investigation for underlying cardiac disease. Men also develop coronary atherosclerosis 10 years earlier than women [86]. The weight of impact which this societal factor imposes on the reported sex differences of SCD incidence is limited when we consider that such warning symptoms are absent in 80% of young athletes who experience SCD [87]. The interplay between these genetic, hormonal, and environmental mechanisms which determine the sex differences of SCD risk is complex and remains poorly understood.

Why do athletes develop ventricular arrhythmias?

Myocardial fibrosis

Myocardial fibrosis (MF) occurs through tissue injury and subsequent cardiac remodeling which is most commonly associated with diseases such as heart failure, CAD, and hypertension. Patients with MF, identified through late gadolinium enhancement (LGE) by cardiac magnetic resonance imaging (cMRI), demonstrate a higher prevalence of VA and adverse cardiac outcomes [88,89].

A higher reported prevalence of MF in endurance athletes compared with sedentary controls was first reported a decade ago [90–92]. Patterns of MF are typically classified as ischemic and nonischemic. In a systematic review of 65 athletes with MF, LGE was characterized as nonischemic, localized at the septum or RV, and represented between 1% and 3% of the myocardium [93]. The pattern of MF in athletes varies from that in the general population, which may be relevant to the underlying mechanisms and clinical prognosis [93].

Only recently have studies evaluated the prevalence of MF in female athletes. A cohort of 54 male and 29 female master triathletes were evaluated with cMRI and compared with 36 sedentary controls [94]. A significant number (17%) of male athletes were identified with focal nonischemic MF compared with none in female counterparts. MF was associated with exercise-induced hypertension and the duration of which the athletes raced. It is worth noting that the female group engaged in significantly shorter distances of exercise and demonstrated lower levels of fitness compared with male counterparts. Similar sex patterns of MF were identified in a study of 152 master athletes (29% female) and 92 controls who were matched for age, sex, and 10-year risk of CAD. MF was confined to athletes only (14%), with all but one case identified men [72].

The clinical significance of MF was evaluated in a study of 158 master athletes (29% female). Consistent sex patterns were described with overt (not confined to RV insertion points) MF identified in 15% of male athletes compared with 2.2% female athletes and none of the healthy controls. Fibrosis, most commonly of a nonischemic pattern, appeared detrimental, given the significant association with NSVT [95]. The causal relationship between MF and arrhythmia is further supported by myocardial biopsy findings in athletes investigated for VA and autopsy findings of athletes who have experienced SCD [93,96,97].

The mechanism of MF in endurance athletes remains elusive; however, occult coronary disease (discussed later in this chapter) [72], silent myocarditis [98], pulmonary pressure overload [99], repetitive microinjury with elevated cardiac biomarkers [100], hypertension [94], and genetic predisposition have all been proposed as contributors (Fig. 29.6).

Assuming nonischemic MF provides a substrate for VA in athletes [72,101], the higher reported prevalence of fibrosis in male athletes may explain the sex differences in reported risk of SCD. More research is required to develop our understanding of the pathogenesis and prognostic significance of MF in otherwise healthy athletes.

Coronary atherosclerosis

Regular exercise offers a desirable risk profile for coronary atherosclerosis and is associated with a 50% reduction in adverse outcomes from CAD [102]. Despite this, CAD is recognized as the leading cause of SCD in master athletes, accounting for approximately two-thirds of cases [90,103,104]. The last three decades has observed an exponential risk in the number of middle-aged and older individuals competing in marathon and ultraendurance events. Evaluation of this growing population has identified a higher than predicted prevalence of CAD compared with sedentary controls, even after adjustment for conventional CAD risk factors [72,105–108]. This has led researchers to propose that endurance exercise may play a contributory role in the development of CAD in otherwise low-risk individuals. In a British study investigating the presence of subclinical CAD in master athletes, 152 athletes (29% female) with a low-risk profile for atherosclerosis were compared with 92 controls matched for age, sex, and risk. A significantly higher prevalence of coronary plaques of any luminal irregularity and coronary calcium (>300 Agatston units) was demonstrated in male athletes versus male controls. Coronary plaques in male athletes were predominantly calcified (73%) compared to mixed morphology (62%) identified in sedentary controls. Calcified plaques are thought to offer protection from cap rupture and acute myocardial infarction, although such adverse outcomes were not formally assessed in this study. The prevalence of CAD was similar between female athletes and controls. Another large Dutch study, published at the same time, examined the relationship between

coronary artery calcification and exercise dose in 284 male athletes. Over half of the athletes (53%) had a CAC > 0. Athletes performing >2000 MET mins of exercise per week had a greater CAC than athletes performing less exercise. As with the British study, athletes performing the greatest amount exercise had a more benign composition of coronary plaques [106]. In contrast, a study comparing 26 female veteran marathon runners (average of 47 previous races) failed to identify any differences in patterns of CAD versus matched sedentary controls [109].

The exact mechanism for SCD in male master athletes remains poorly understood. Ischemic VA provides the final common pathway although the triggers for this remain unclear. Proposed triggers include hemodynamic effects of plaque vulnerability, oxidative stress, thrombogenicity, metabolic and electrolyte factors, and sympathetic activation (Fig. 29.6). Additional studies in larger cohorts of men and women are required to clarify the mechanisms and clinical implications of subclinical CAD in master athletes.

Right ventricular remodeling

The structural changes of the "athlete's heart" appear most pronounced on the right-sided cardiac chambers. Indeed, intense exercise imposes a disproportionately larger degree of RV wall stress and fatigue compared with the LV which creates potential for a diagnostic overlap with ARVC [110,111]. RV contractility initially increases in proportion to pulmonary artery pressures during the early phases of intense exercise [112]. When intense exercise is sustained for several hours, however, RV dysfunction occurs with a corresponding elevation of cardiac biomarkers including B-type natriuretic peptides and cardiac troponin [91,110]. Researchers have since proposed that repeated insults to the RV inflicted by endurance exercise results in irreversible cardiac remodeling which may provide a substrate for VA [97].

The concept of "exercise-induced ARVC" was first reported in a study of 46 young endurance athletes who presented with complex VA including NSVT and aborted sudden cardiac arrest [97]. The majority (80%) of VA observed over the 5-year follow-up period originated from the RV, which was attributed to the high burden of RV dysfunction. Despite a subset of these athletes meeting diagnostic criteria for ARVC, the prevalence of ARVC-causing genes was unexpectedly low [113]. The gene-elusive nature of this phenotype described in various studies since [114,115] has led researchers to speculate that endurance exercise plays a central etiological role in the promotion of disease.

Evidence for this ARVC phenotype being purely exercise-induced remains limited when we consider that these small studies are largely derived from highly selected cohorts of diseased athletes. Selection bias in these studies is a likely possibility as athletes with a proven ARVC phenotype are usually excluded from participation. Evidence for exercise accelerating the phenotype of ARVC in genetically predisposed athletes has attracted more recent attention. The extent of RV remodeling and incidence of VA is higher in desmosome mutation carriers who engage in regular exercise and as a result reaches an earlier diagnosis compared with sedentary counterparts [115–117]. The interplay between environmental factors such as exercise and genetic abnormalities appears complex. Studies suggest that exercise may cause and accelerate forms of ARVC although whether these two entities form part of a clinical continuum remains unclear (Fig. 29.6).

Conclusion

Long-term athletic training leads to a constellation of electrical, structural, and functional remodeling which forms the "athlete's heart." Paradoxically, however, there is mounting evidence that long-term endurance exercise is associated with an increased risk of AF. Clear sex patterns exist in the cardiac response to exercise and in the dose–response relationship between exercise and risk potentially adverse outcomes. Female athletes show less profound electrical and structural remodeling in response to vigorous exercise training. Females are also at a lower risk of SCD, MF, coronary artery calcification, and RV remodeling than male athletes. These sex differences are likely determined by a complex interplay of genetic, hormonal, and environmental mechanisms, which remain poorly understood. The modern era of sport continues to see a rise in both female and endurance athletes. This growing population will provide researchers with greater opportunities for larger prospective longitudinal studies to better evaluate sex influences on the relationship between exercise and arrhythmia.

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Part IX

Cardiomyopathies and inherited disorders

Chapter 30

Hypertrophic cardiomyopathy

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Introduction

Hypertrophic cardiomyopathy (HCM) is a disorder characterized by hypertrophy of the left ventricular (LV) myocardium without ventricular dilatation. It occurs without a secondary cause such as hypertension or systemic disease and is marked by variable morphologic, clinical, and hemodynamic abnormalities. Clinically, it can present with typical angina, dyspnea, arrhythmias, or by sudden cardiac death (SCD). The pathophysiology is generally an interplay of LV outflow obstruction, myocardial ischemia, diastolic dysfunction, atrial fibrillation (AF), mitral regurgitation, and myofibril abnormalities, which can lead to SCD. Electrocardiographic abnormalities traditionally show ST segment depressions, T-wave inversions, or pathologic Q waves. This chapter will focus on the sex differences in the disorder of HCM as it pertains to clinical practice.

Epidemiological features

Diagnosis and prevalence

HCM is defined clinically as an increase in myocardial wall thickness of >15 mm (or >13 mm with a first-degree relative with HCM) on either echocardiography or cardiovascular magnetic resonance (cMR) imaging, in the absence of an identifiable organic load condition such as valvulopathy, hypertension, or other systemic disease [1]. HCM is the most prevalent monogenic inherited cardiac disease and the most common form of cardiomyopathy [2]. Approximately 2−5 per 1000 people in the developed world have HCM and of those 40%−70% have obstructive disease (LV intracavitary gradient >30 mmHg at rest) [1]. However, the true incidence is likely higher as many patients with HCM go undiagnosed because of mild or absent symptoms and lack of routine screening. The actual incidence is unclear; echocardiographic-based epidemiologic studies have shown a prevalence of 1 case per 500 persons in the general population [3]. However, when clinical and genetic considerations are taken into account, the prevalence is approximately 1 in 200 [4]. It appears that the disease is widely underdiagnosed globally; within the United States, an estimated 10% of the possible HCM patients have been identified (Fig. 30.1). Disproportionally, women and minorities have been under recognized and undertreated in HCM [5]. Excess HCM-related sudden deaths in black male athletes have been reported [6]. Comparison with female athletes is not available.

As HCM is predominantly caused by autosomal dominant mutations, equal distribution between the sexes would be expected. Cohort study data, however, suggest that men may be more commonly afflicted by HCM (55%−74% male) [2]. However, females diagnosed with HCM were on average 9 years older than their male counterparts [7] and were at an increased risk of heart failure and death [8].

Global burden

Although HCM was initially recognized only in developed nations in North America and Europe, improved diagnostic sensitivity and increased prevalence of screening have broadened the scope of the disease to a global scale (Fig. 30.1). HCM has been identified in patients of 122 different countries ranging from the polar regions to the equator [9]. The absence of HCM in the remaining nations likely represents a deficiency in medical resources rather than lack of the disease itself. It is estimated that as many as 20 million people worldwide may be affected by HCM; however, many patients go undiagnosed, particularly in

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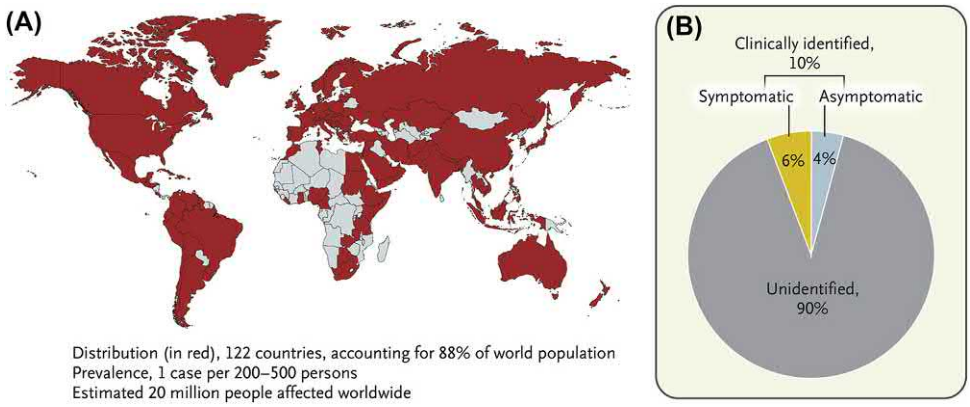

FIGURE 30.1 Epidemiologic features in hypertrophic cardiomyopathy. Panel A: Worldwide distribution of the disease, which likely has a global spread. Reports are not available from some countries. Panel B: Proportions of clinically identified and unidentified cases. *Adapted with permission from Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med 2018;379(7):655–68.*

underdeveloped nations with poor infrastructure and medical resources, because of lack of diagnostic tools or overt clinical symptoms [9]. These missed diagnoses represent significant unrecognized disease burden on the global population. One retrospective analysis of 4591 patients with HCM spread over eight countries showed that patients diagnosed with HCM before the age of 40 years have a 26% incidence of lethal arrhythmia by age 60 years [10]. This infers a large, unrecognized patient population that would benefit from clinical diagnosis and intervention.

Genetics

The most common (>60% of patients) form of HCM results from mutations of autosomal dominant sarcomere genes. Several hundred individual mutations have been identified (most commonly in B-myosin heavy chain MHY7 and myosin binding C protein MYBPC3 genes). These genetic defects are typically inherited and, however, can be sporadic in nature. Patients with multiple distinct genetic defects are observed to have more severe disease [11]. One-third of HCM patients have no identified genetic etiology to their disease. The remaining 10% of patients result from hereditary syndromes, neuromuscular disorders, and storage diseases resulting in accumulation of abnormal substrates that result in increased myocardial fibrosis and remodeling [1]. Studies show that the clinical impact of this genetic heterogeneity is significant. Data from the SHaRe registry (Sarcomeric Human Cardiomyopathy Registry) demonstrate that HCM patients with sarcomere defects showed clinical disease at an earlier age as well as increased incidence of heart failure and arrhythmias. Compared to HCM patients without sarcomere defects, these patients have an increased risk (29% vs. 14% by age 50) of cardiac arrest, heart transplant, implantable cardioverter defibrillator (ICD) implantation, AF, stroke, and New York Heart Association (NYHA) class III/IV heart failure [10].

Sex appears to play a modulating role in phenotypic variability in HCM. Mutations in MYBPC3, MYH7, and TNNI3 proteins have all been associated with either later onset of disease or increased prevalence of incomplete penetrance in females as compared with males [12], which may explain the observational data showing women tend to be older at age of diagnosis. Animal model studies suggest that endocrine factors, particularly estrogen levels, may be protective against development of myocardial hypertrophy [13].

In one recent study determining the effect of sex on genetic mutations, female patients with HCM presented at more advanced age with different clinical, phenotypic, and genetic status, while independent association of female sex and outcome was noted [14].

Pathophysiology

Although many genetic predispositions have been identified, the underlying molecular mechanisms behind HCM are not well described. Several pathways have been proposed, including intracellular energy depletion, alterations in force development/transmission, abnormal calcium homeostasis, and dysfunctional vascular endothelium [15]. Regardless of cause, HCM involves cardiac myocyte hypertrophy, usually most pronounced in the LV and asymmetric in nature. Hypertrophy of the septum is most predominant; however, isolated LV free wall, apex, or anterolateral wall, or even concentric hypertrophy is also observed [11]. Approximately 30% of patients are observed with right ventricular hypertrophy as well (maximum wall thickness > 8 mm) and rarely right ventricular outflow

obstruction in addition to LV pathology. Histopathology reveals cardiac myocyte disarray and increased interstitial fibrosis (Fig. 30.2 Panels A and B) [2]. This myocardial disorganization and subsequent risk for arrhythmia is thought to explain the increased risk of SCD, approximately 1% per patient-year, seen in HCM patients [2].

The coronary vasculature is not exempt from adverse changes—smaller intramural arteries show intimal and medial smooth muscle hyperplasia and medial fibrosis, resulting in luminal narrowing. Myocardial bridging also plays a role in narrowing the epicardial arteries. In addition, ischemia plays a role in risk of arrhythmia in HCM patients. Marked LV hypertrophy and left ventricular outflow tract (LVOT) obstruction both contribute to increased myocardial oxygen demand. Intramural small-vessel hyperplasia, myocardial bridging, abnormal myocyte architecture, massive myocyte hypertrophy, and abnormal intramural microcirculation all contribute to increased diffuse microcellular ischemia in HCM. Coronary microcirculation is further impaired by diastolic dysfunction and subsequent increased left ventricular end diastolic pressure (LVEDP), which contribute to extend the compression of microvasculature and limit overall blood flow to cardiac myocytes [11].

Diastolic dysfunction is a cornerstone of HCM clinical disease presentation. The interstitial connective tissue is also overly prolific with extensive fibrosis and is thought to account for the reduced LV chamber compliance and diastolic dysfunction seen. Increased LVOT obstruction, in combination with impaired intracellular calcium reuptake and nonuniform ventricular contractility, results in impaired ventricular relaxation [11]. This LVOT obstruction results not only from LV hypertrophy but also from mitral valve (MV) pathology thought to be resultant

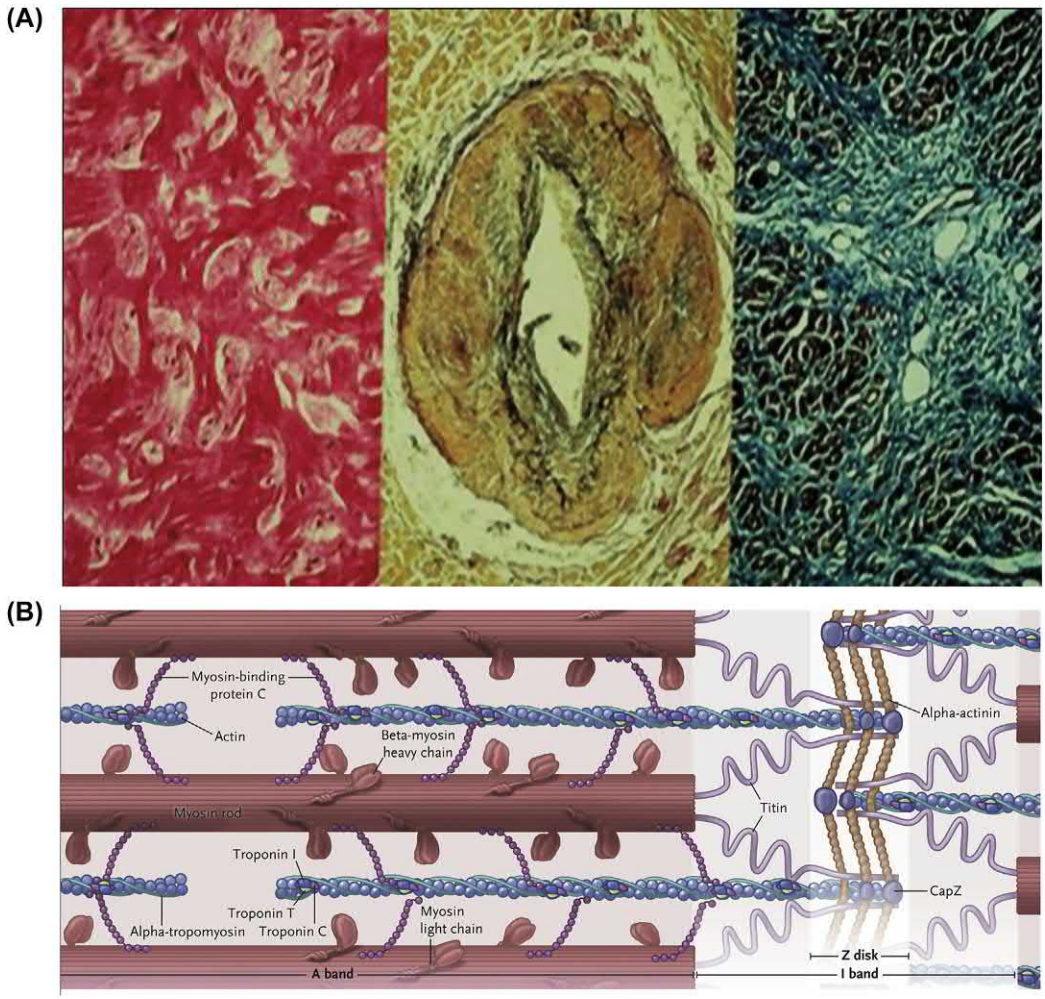

FIGURE 30.2 Pathophysiologic features in hypertrophic cardiomyopathy. Panel A: Histopathology features of hypertrophic cardiomyopathy including disorganized architecture of the left ventricular myocardium (left), an abnormal intramural coronary artery with thickened wall and narrowed lumen (center), and a myocardial scar (right). Panel B: A diagram of a cardiac sarcomere. *Adapted with permission from Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med 2018;379(7):655–68.*

from the underlying genetic defects (anterior MV displacement, elongated MV leaflets, increased anterior MV leaflet area, papillary muscle abnormalities, degenerative and myxomatous valves) [11].

Sex differences in the clinical picture of HCM also exist at the pathophysiologic level. Women with HCM are reported to have lower maximal LV wall thickness, smaller left atrium (LA) and LV end-diastolic dimensions, and increased LV outflow obstruction as compared with their male counterparts [7]. Another retrospective analysis of patients with HCM found a lower remodeling index (LV mass/end-diastolic volume) in women compared with men [8], possibly related to increased levels of fibrosis seen at necropsy or late-gadolinium enhanced cMR imaging [2]. These discrepancies may be explained by the large portion of patients with HCM of unknown genetic cause. However, certain underlying factors, such as increased risk of SCD, remain equal between the sexes [2]. Female patients tended to be older at the time of myectomy and showed greater impairment of diastolic function [16]. In addition, women showed increased LV and left atrial remodeling and increased titin compliance with more interstitial fibrosis.

Diagnosis

A complete workup for diagnosing HCM involves utilization of both electrocardiographic and echocardiographic data. Both diagnostic modalities have unique criteria for the diagnosis of HCM. Initial evaluation of HCM should include an ECG, which is abnormal in up to 95% of patients [17]. The electrocardiogram (ECG) for a majority of patients with HCM shows evidence of LV hypertrophy (e.g., tall R-waves V2−V5) and widespread ST depression and T wave changes (Fig. 30.3, Panel A). There are, however, variations in the ECG among patients with apical HCM such as diffuse symmetric T-wave inversions throughout the precordial leads [17]. Part of the diagnostic/prognostic evaluation may involve a 24-h ambulatory monitor (i.e., Holter monitor) to aid in screening for nonsustained ventricular tachycardia, which generally adds prognostic information about the risk for SCD.

ECG differences among men and women

Sex-specific criteria have enhanced the accuracy of ECG recognition of LV hypertrophy in the general population [18−21]. However, there have been few studies using sex-specific voltage criteria or adjusting for sex when specifically studying men and women with HCM [18−21]. Use of the Cornell voltage criteria, QRS duration, and the products of QRS voltage and duration have been shown to be significantly less accurate in diagnosing women compared with men with HCM [18]. This lower accuracy among female patients may be due to a lower QRS voltage and QRS duration per gram of LV mass among women when accounting for body habitus and cardiac chamber dimensions [18].

Morphologic features of imaging studies

Left ventricular hypertrophy

HCM is characterized by LV hypertrophy, diastolic dysfunction, and myocardial fibrosis [22]. Echocardiography allows for definitive diagnosis of HCM via visualization of the hypertrophied segment of the left ventricle (Fig. 30.3, Panels C−F). Specifically, diagnosis of HCM can be confirmed when such myocardial hypertrophy (>15 mm or >13 mm for first-degree relatives) is noted without concurrent wall dilatation or a clinical syndrome that would otherwise cause the degree of hypertrophy noted [16,23]. Among patients with HCM, the area of abnormal hypertrophy most often occurs in the anterior septum; however, the posterior septum and anterior free wall are also often involved as well [24]. Nevertheless, HCM carries vast heterogeneity in its condition and hypertrophy may occur throughout any segment; such variations are noted even among relatives known to have the same HCM genotype. Furthermore, LV noncompaction cardiomyopathy can be similar to the apical form of HCM and requires distinction [25].

Given that HCM involves sarcomere gene mutation and carries an autosomal dominant inheritance pattern, the prevalence of HCM in the general population is expected to be similar among men and women [7]. However, within the latest cohort studies, women represent a minority of patients with HCM, with percentages ranging from 26% to 45%, suggesting lower disease penetrance in women [7,16,26]. However, this underrepresentation may be in part due to a delay in diagnosing women until later in their disease course. Prior data show women are often diagnosed on average 9 years later with significantly more symptoms compared with men [7,16,27].

The heterogeneous distribution of where hypertrophic tissue may arise in the left ventricle among patients with HCM makes traditional imaging algorithms aimed at measuring LV mass limited [25]. Thus, several echocardiographic indexes have been proposed to aid in the assessment of LV hypertrophy in these patients [24,25,28,29].

Earlier diagnostic criteria utilized M-mode to delineate asymmetrical septal hypertrophy, systolic anterior motion of the mitral valve (SAM), small LV cavity diameter, septal immobility, and early closure of the aortic valve [23,25,30]. A thickness measured >15 mm at the level of the septum and/or the free wall of the left ventricle is

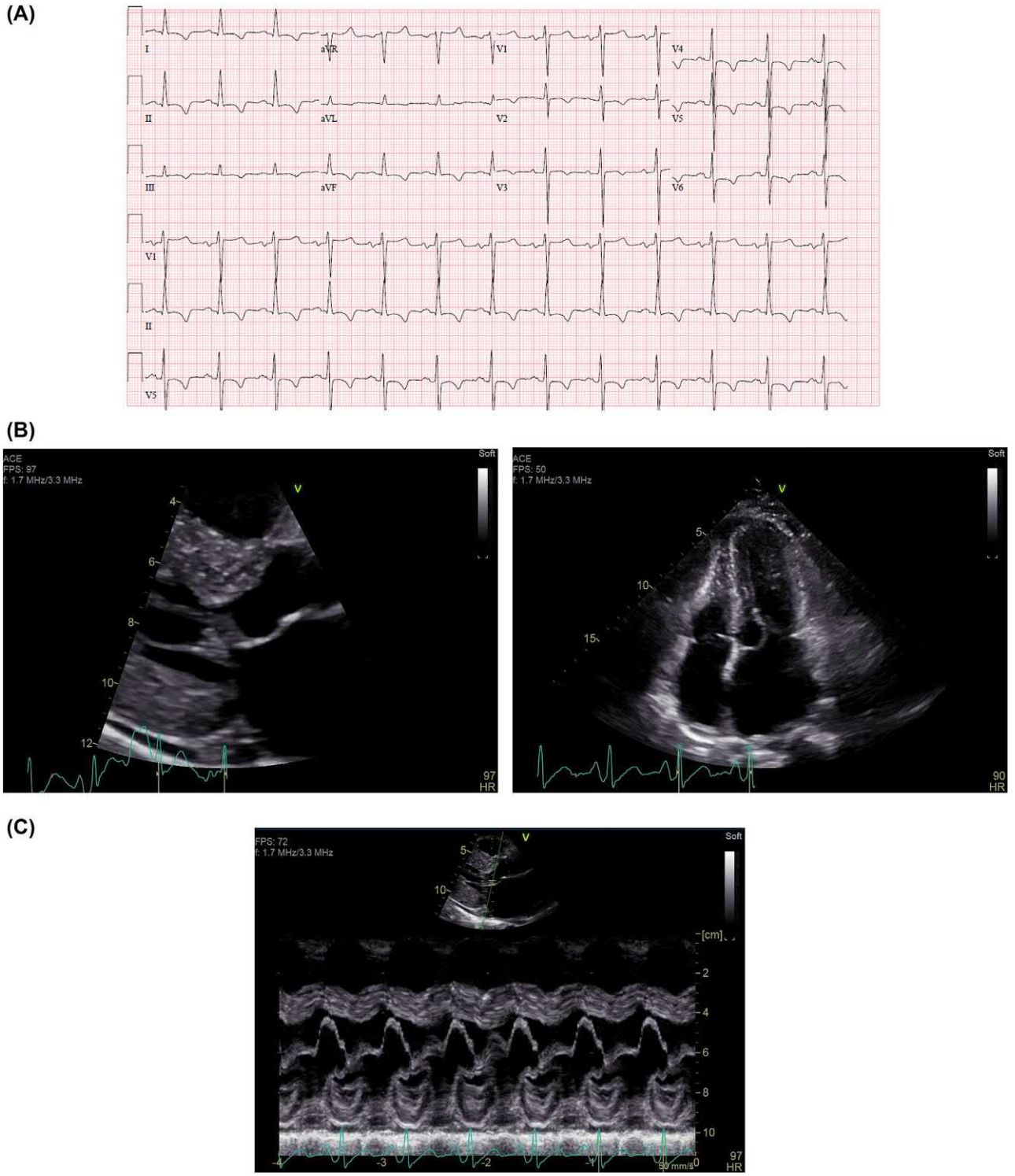

FIGURE 30.3 **Morphologic features of hypertrophic cardiomyopathy (HCM) imaging.** Panel A: Typical electrocardiographic features in HCM with marked left ventricular hypertrophy and diffuse T wave changes. Panel B: Echocardiographic features of HCM. Parasternal long-axis view and apical four-chamber views of a hypertrophied nondilated left ventricle with diffuse thickening of the left ventricle. The mitral valve is thickened because of distortion from elevated left ventricular outflow tract (LVOT) gradients. The left atrium is significantly dilated. Panel C: M-Mode of the mitral valve demonstrating typical systolic anterior motion of the mitral valve. Panel D: Diastolic dysfunction present with shortened deceleration time and low tissue Doppler velocities. Panel E: Elevated, late peaking gradients with the LVOT, worsening with the Valsalva maneuver or exercise captured on Doppler echocardiography. Panel F: Four-chamber view of diastole (left) and systole (right) with echocardiographic contrast demonstrating a left ventricular apical aneurysm. Panel G: Cardiac MR characteristics of HCM demonstrating a four-chamber view with a left ventricular apical aneurysm and midventricular variant hypertrophy (left) and short axis view with late gadolinium enhancement of the septal segments demonstrating fibrosis (right).

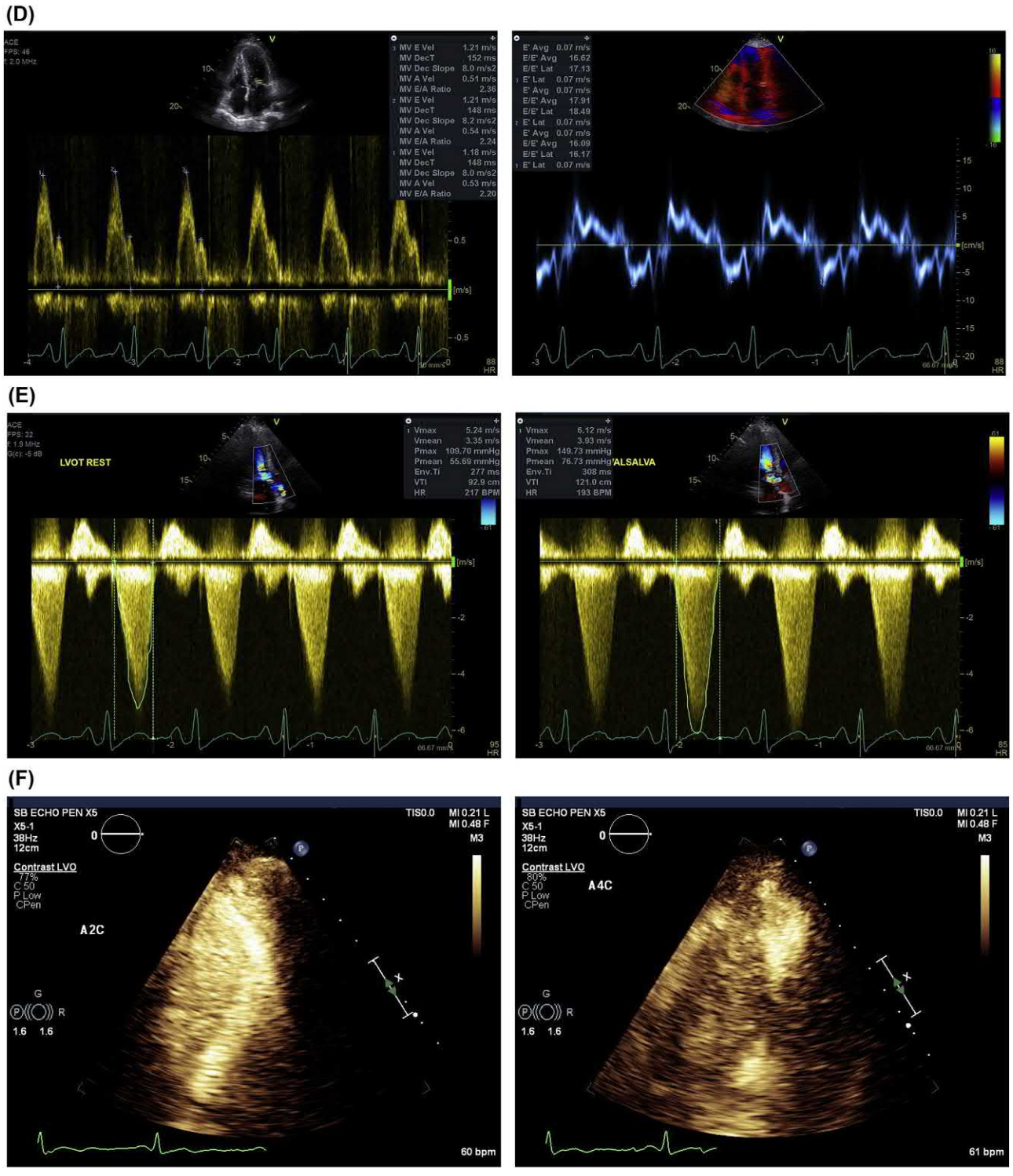

FIGURE 30.3 cont'd

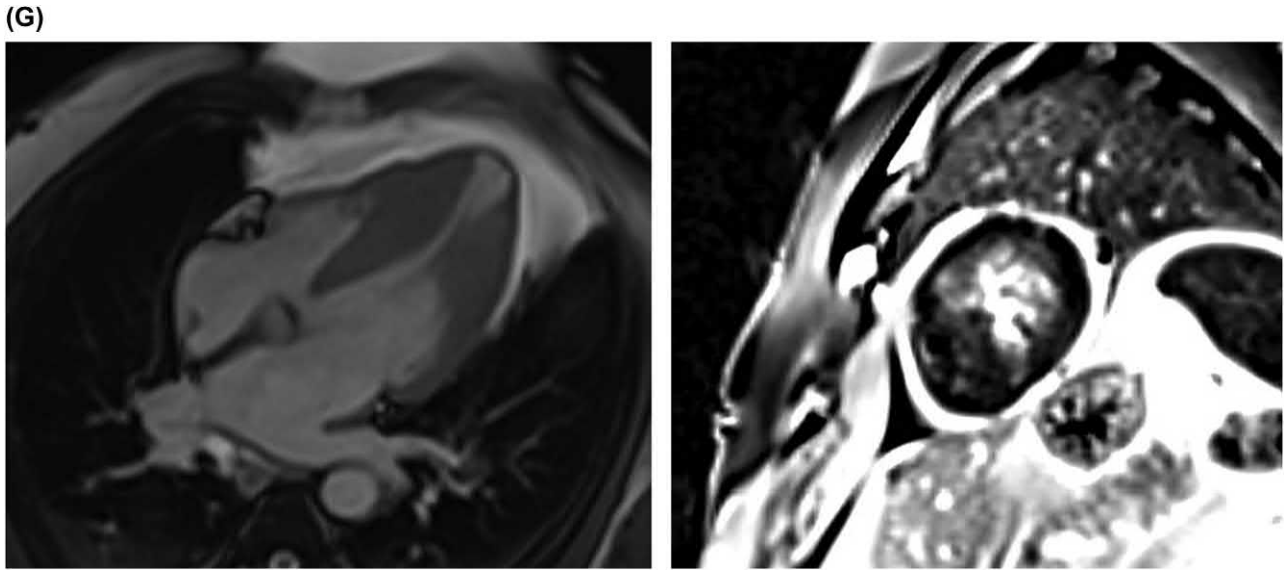

FIGURE 30.3 cont'd

considered abnormal in patients with no known family history of HCM. In addition, asymmetry can be diagnosed too if the septal to free wall thickness ratio is between 1.3 and 1.5 [25].

Outflow obstruction

SAM is characterized by peak anterior motion of the mitral valve leaflet before the posterior wall achieving maximal movement in the opposite direction. M-mode can be used to assess the mitral valve's motion, which with septal hypertrophy can help to diagnose HCM (Fig. 30.3). However, other conditions that can cause hypertrophy such as chronic systemic and renovascular hypertension, Fabry's disease, and Friedreich's ataxia should also be considered in such findings [25,31–34].

Echocardiographic features

Among the most clinical important images to obtain is the measurement of the maximal wall thickness, which should be evaluated across all segments [35]. There are several prior studies indicating higher LV volume and mass among men compared with women after adjusting for blood pressure, fat-free mass, and other parameters [36–40]. These differences among men and women carry notable clinical and epidemiological ramifications if not accounted for. Historically, patients with HCM had shown no clear evidence of echocardiographic differences in maximal wall thickness or distribution of the hypertrophy between sexes [24]. However, more recent data demonstrate women on average have smaller end-diastolic volume, more diastolic dysfunction, and less ventricular remodeling compared with male counterparts [7,16,22,41]. Furthermore, apical hypertrophy has also been more often noted among men [26,42–46], whereas outflow obstruction has been more often seen among women which may be associated with the smaller ventricular size [26]. Echocardiographic assessment with strain rate imaging and digital speckle tracking has provided mechanistic and functional insights into diastolic dysfunction, but has not yet added to disease prognosis and management. Future studies on sex-specific imaging studies may provide further insights into risk stratification and prognosis.

Cardiovascular magnetic resonance imaging features

Owing to its high-resolution volumetric reconstruction of the LV chamber, cMR imaging allows for accurate LV wall thickness, dimensions, and morphology [47]. These properties have been useful in the determination of the diagnosis of HCM, particularly when the diagnosis is unable to be made clinically or echocardiographically (Fig. 30.3, Panel G). cMR provides accurate determination of wall thickness as well as enhanced risk stratification, through identification of myocardial fibrosis with late gadolinium enhancement (LGE) [48]. Sex-specific data on this subject are not yet available.

Clinical features and management

Sudden cardiac death

In patients with HCM, there is an increased risk of developing atrial and ventricular arrhythmias, attributed to the

structural and physiological changes in the myocardium. Even in the healthy heart, the QT interval differs in males and females, but this difference is only noted after puberty. The QT interval of males shortens as men age from adolescence and this is most likely because of the ventricular repolarization shortening effect from testosterone [2]. The risk factors for SCD in patients with HCM include (1) previous history of ventricular fibrillation or sudden cardiac event, (2) family history of sudden cardiac event, (3) unexplained syncope, (4) nonsustained ventricular tachycardia, (5) LV wall thickness greater than or equal to 30 mm, (6) impaired blood flow response to exercise, and (7) LGE on cMR (Fig. 30.4) [2]. An LV apical aneurysm (Fig. 30.3) regardless of the size or patient's age also warrants consideration for implantation of a defibrillator for primary prevention [9]. Patients with HCM who do not have any of these risk factors may still be at increased risk of SCD (approximately 1% per year) and therefore those with risk factors can be expected to be at an even higher risk of SCD. A multicenter study including 969 patients from Italy and the United States did not show any difference in the proportion of male patients and female patients who received an ICD [7]. With the available data, sex does not seem to affect the rate of SCD, as similar rates were present in both men and women.

The decision of whether or not to implant a defibrillator requires consideration of possible device-related complication (3%–5% per year). Subcutaneous defibrillators have the advantage of protecting the venous system in younger patients and avoid leads and their complications. However, their efficacy in treatment of arrhythmias in HCM remains unclear, as is any sex-specific data.

Iatrogenic rhythm disorders

In patients who have LV outflow obstruction, treatment via septal reduction can increase the risk of arrhythmias [2]. Septal reductions can be achieved either through alcohol septal ablation or surgical septal myectomy. Alcohol septal ablation causes infarction of the basal interventricular septum, which may contain the right bundle branch, and consequently, 36% of patients develop right bundle branch

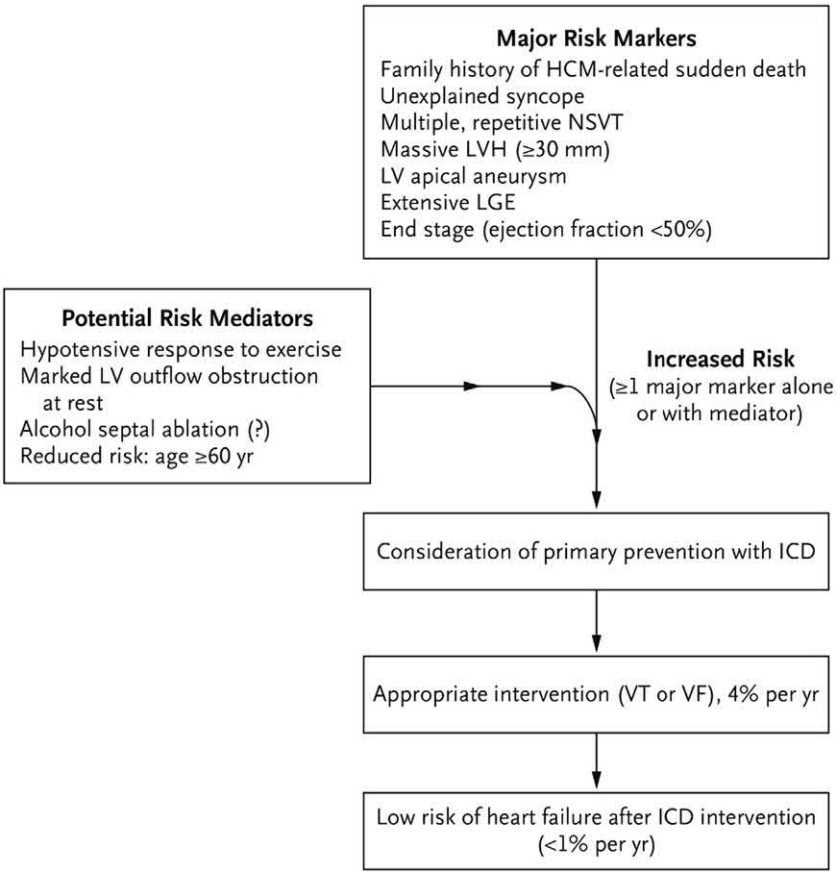

FIGURE 30.4 Sudden death risk stratification in hypertrophic cardiomyopathy (HCM). Selection of patients for prophylactic implantable cardioverter defibrillator (ICD) placement is based on major markers of risk, sometimes in association with potential risk mediators. LVH denotes left ventricular hypertrophy, NSVT nonsustained ventricular tachycardia (on ambulatory monitoring), VT ventricular tachycardia, and VF ventricular fibrillation. *Adapted with permission from Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med 2018;379(7):655–68.*

block and in 12% the left bundle branch may also be involved and ultimately lead to complete heart block [2]. In surgical septal myectomy, septal tissue is removed from the anterior portion of the interventricular septum with the development of a left bundle branch block in about 40% of the patients who undergo this procedure [2]. About 3% develop complete heart block [2]. As alcohol septal ablation causes infarction, the scar can be a substrate for arrhythmias that would require implantation of an ICD [2]. Surgical septal myectomy is therefore the preferred option for those with HCM who are refractory to medical management and may be older [2]. No sex differences have been found in those with HCM and iatrogenic rhythm disorders [2].

Atrial fibrillation

In patients with HCM, AF is the most common sustained arrhythmia [9]. The incidence of AF in those with HCM is approximately 2% per year with a prevalence of 20%–25% [2]. This arrhythmia is an independent risk factor for mortality in those with HCM as it increases the risk of HCM-related deaths fourfold. The mortality is 3% per year [2].The frequency of outflow obstruction was similar in those patients with AF and without AF [49]. Left atrial enlargement, which is described as greater or equal to 45 mm, can be a strong predictor of AF [50]. This finding is common in HCM and is most likely a sequelae of the thickened, noncompliant ventricles resulting in impaired diastolic function [49]. The loss of atrial contribution to ventricular filling can contribute to the adverse consequences found in those with marked LV hypertrophy and diastolic dysfunction. In comparison to HCM patients in sinus rhythm, there has been an association between AF and adverse outcomes including heart failure, stroke, and death in HCM [51].

In the absence of HCM, males are associated with an increased risk of developing AF. In those with HCM, AF is an independent risk factor for mortality, and this is thought to be propelled by the associated consequences of AF including heart failure and stroke-related death [2]. Risk factors for AF are more common in this population with HCM than the general population including increased left atrial size, sleep apnea, ventricular myocardial fibrosis, and inhomogeneous atrial conduction [2]. Although the male sex is associated with an increased risk of developing AF, this difference was not conveyed in the actual prevalence of AF in males and females [26].

The burden of AF also does not seem to significantly affect the outcomes as there was no difference in mortality found between those with paroxysmal AF compared with permanent AF [49]. The prevalence of stroke was similar in those who had multiple episodes of AF versus a single episode of AF [49]. LGE quantification can be used to assess fibrosis in the LA with cMR imaging. In non-HCM patients with AF, those who are in permanent AF have greater amounts of LA-LGE.

Heart failure

A large proportion of patients will develop heart failure symptoms of varying degrees of severity, usually presenting as exertional shortness of breath and fatigue. Women have been underrepresented in clinical cohorts but on average tend to older with more severe symptoms upon presentation. It is unclear whether this is because of societal reasons, sex bias by healthcare professionals, or a true sex-specific difference in pathophysiology.

For most patients with chronic heart failure with HCM, the main cause is LVOT obstruction at rest and with exercise, which leads to elevated LV filling pressures and secondary mitral regurgitation. Heart failure is often associated with diastolic dysfunction, pulmonary hypertension. Medical therapy is the first option for symptom control (β-blockade agents, calcium channel blockers, and negative inotropic medications such as disopyramide). For patients with disabling symptoms, advanced NYHA Class, and elevated LVOT gradients, primary transaortic septal myomectomy or in selected patients, alcohol septal ablation can be considered. Dual-chamber pacing with complete ventricular preexcitation through a short atrioventricular delay to reduce outflow tract gradient is not considered primary therapy for obstruction [52].

For patients without obstruction, disease management focuses on prevention of arrhythmias and treatment of progressive end-stage heart failure. For those who are refractory to medical management, HCM patients may ultimately become candidates for heart transplantation. One of the few factors that predict end-stage heart failure is extensive myocardial fibrosis. Cardiac resynchronization therapy can offer relatively short-term symptom relief before transplantation [53].

Prognosis

The long-term prognosis in HCM has evolved over the last 50–60 years, from a disorder with a grim prognosis to a treatable disease with a low mortality. It is now apparent that HCM is a relatively common disorder, with the majority of patients achieving normal or near-normal life expectancy. For those HCM patients who experience, or are at risk for, disease-related complications, several strategies

have altered the natural history of their outcomes. Those include implantable defibrillators, heart transplantation, external defibrillation/therapeutic hypothermia, advances in surgical myectomy, and alcohol ablation (Figs. 30.5 and 30.6). More recent cohort studies using more contemporary management strategies have revealed significant improvement in survival, near-normal life expectancy, with a low HCM-related mortality of 0.5% per year across all ages [3]. This includes younger patients (children and young adults) who were typically thought to have a more aggressive course (Fig. 30.7).

In a cohort study from Italy and the United States followed for over 6 years, there were sex-related differences in clinical outcomes [7]. Female patients with HCM had a 50% greater risk of progression to severe congestive heart failure symptoms or death from heart failure over male patients, a finding that was independent of age and functional class (Fig. 30.8). In comparison to male patients in this cohort, the more progressive clinical course of HCM in female patients may have been explained in part by the greater prevalence of LV outflow obstruction. In a large HCM referral population, women with HCM presented at

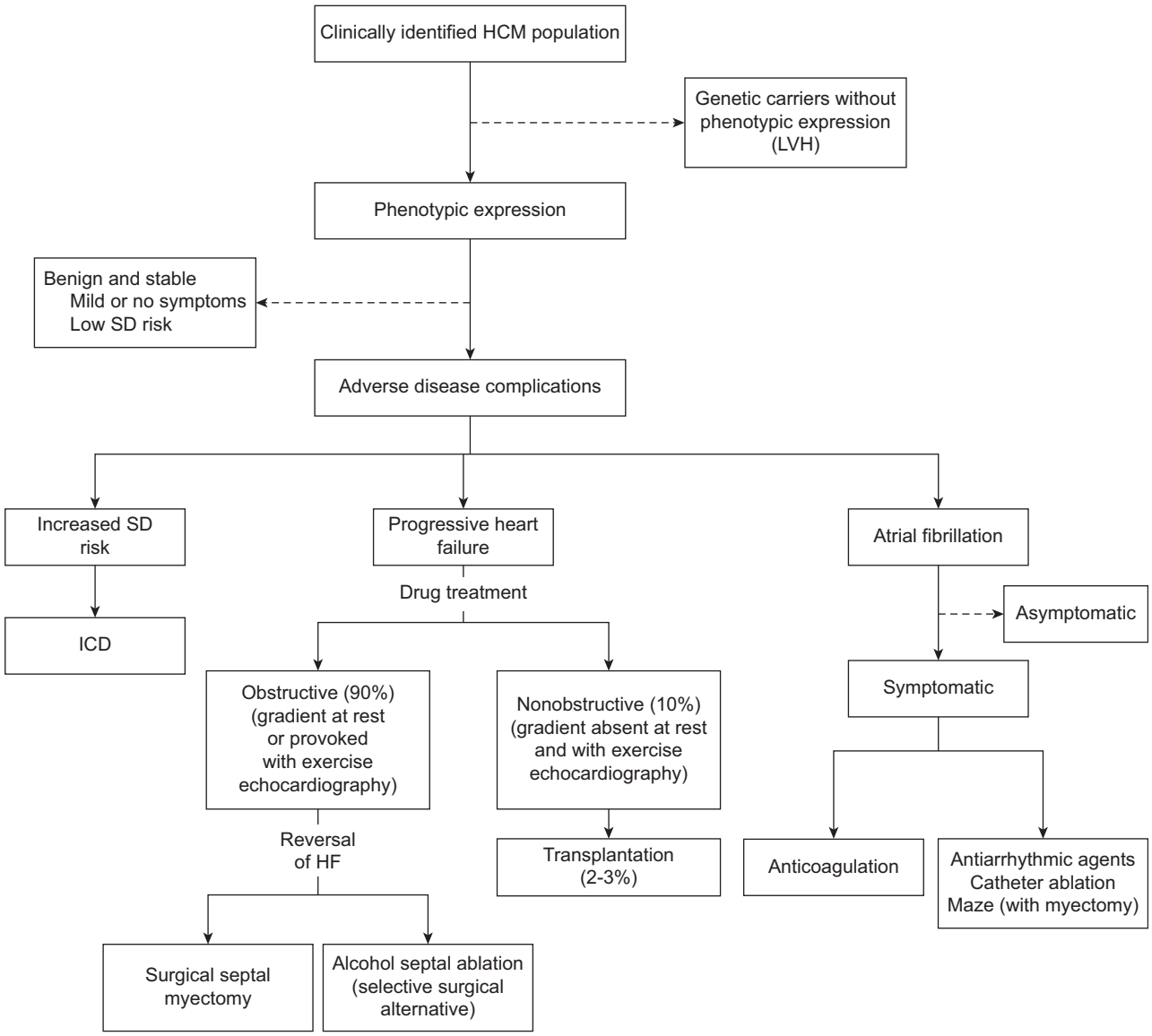

FIGURE 30.5 Management algorithm of hypertrophic cardiomyopathy (HCM). In addition to transplantation, treatments for advanced heart failure (HF) in patients with nonobstructive HCM include cardioactive drugs, cardiac resynchronization therapy, and left ventricular–assisted devices. SD denotes sudden death. *Adapted with permission from Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med 2018;379(7):655–68.*

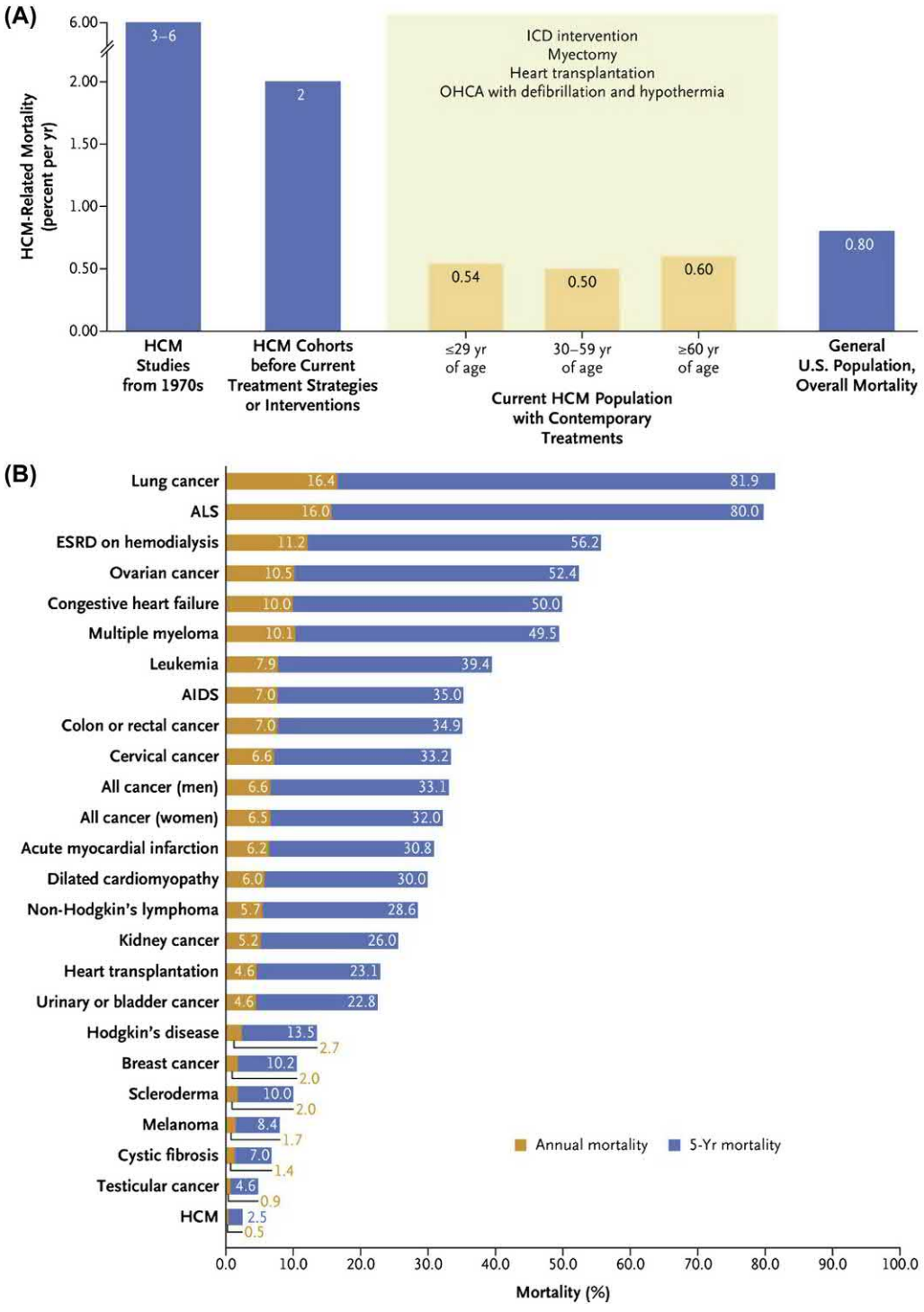

FIGURE 30.6 **Risk of death attributable to hypertrophic cardiomyopathy (HCM) compared with other diseases.** Panel A shows the decrease in mortality over a period of more than 50 years, encompassing various treatment eras. OHCA denotes out-of-hospital cardiac arrest. Panel B shows mortality associated with HCM with contemporary treatment, as compared with mortality associated with other disorders with current treatments. AIDS denotes acquired immunodeficiency syndrome, ALS amyotrophic lateral sclerosis, and ESRD end-stage renal disease. *Adapted with permission from Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med 2018;379(7):655–68.*

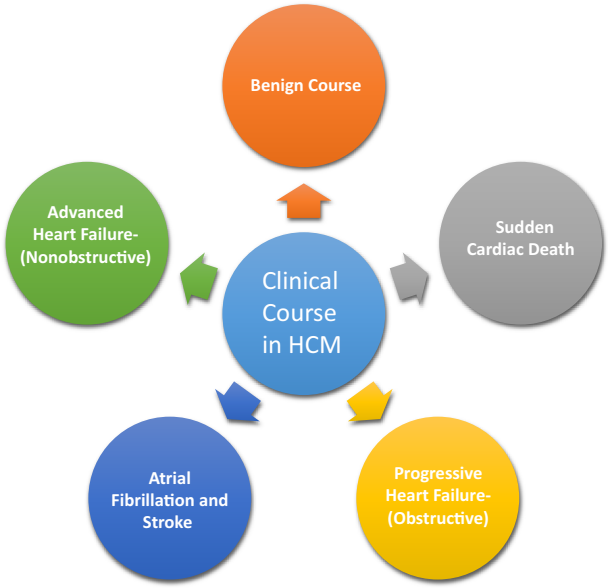

FIGURE 30.7 Potential prognostic pathways in hypertrophic cardiomyopathy. *Modified from Maron BJ, Rowin EJ, Casey SA, Maron MS. How hypertrophic cardiomyopathy became a contemporary treatable genetic disease with low mortality: shaped by 50 years of clinical research and practice. JAMA Cardiol 2016;1(1):98–105.*

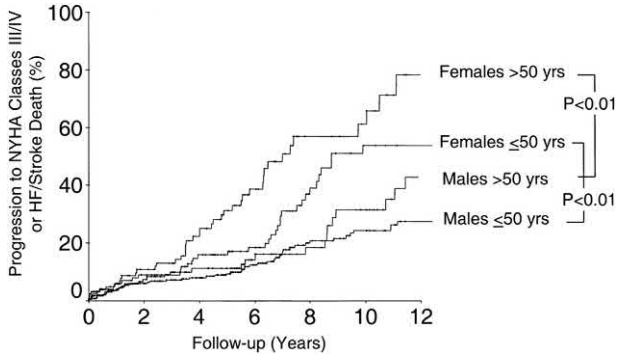

FIGURE 30.8 Sex differences in clinical outcome. Cumulative risk of progression to New York Heart Association (NYHA) functional classes III and IV or heart failure (HF) or stroke death related to age at initial presentation and sex. *Adapted with permission from Olivotto I, Maron MS, Adabag AS, Casey SA, Vargiu D, Link MS, et al. Gender-related differences in the clinical presentation and outcome of hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46(3):480–7.*

more advanced age, with more symptoms and worse cardiopulmonary exercise tolerance. Sex was an important determinant of survival, as women had worse survival in this population [54] and others [55]. Women commonly have smaller LV cavity dimensions and may be more at risk for development of symptomatic LVOT obstruction, and hence more symptomatic heart failure, than men (Fig. 30.9). Moreover, the enhanced susceptibility of female patients to HCM may lead to other sequelae related to the disease itself, such as AF, stroke, and heart failure. Future sex-specific studies are required to study the disease in the contemporary era on a global level.

Special considerations: pregnancy in hypertrophic cardiomyopathy

HCM can affect women of childbearing age and their offspring. Pregnant women with the disease are often diagnosed with HCM for the first time in pregnancy. Owing to rises in cardiac output and increased stroke volume, the left ventricle tends to dilate and allows for decreases in LVOT obstruction, if present. Increased mitral regurgitation often occurs in pregnancy because of increased stroke volume [56]. Patients with the highest risk of deterioration in pregnancy are those with symptoms before pregnancy and those with severe LVOT obstruction (>100 mm Hg) at rest (Table 30.1). In a large administrative dataset within the United States, pregnant women with HCM were at risk for major adverse cardiac events during the hospitalization for delivery, which occurred approximately 23% of cases, most commonly related to heart failure and arrhythmias [57], while in-hospital death was low. Cesarean approach to delivery was common, in approximately 48% of cases. In the prospective worldwide Registry of Pregnancy and Cardiac Disease, major adverse cardiac events most commonly occurred during the third trimester and the postpartum period [58]. Predictors of cardiac events in pregnancy in HCM women are NYHA functional class >2 and signs of heart failure before pregnancy.

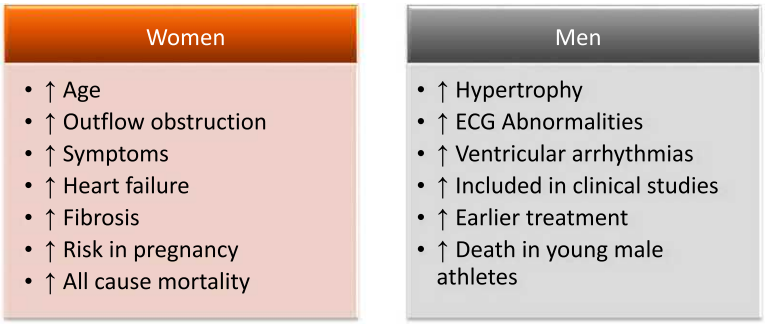

FIGURE 30.9 Sex-specific differences in clinical phenotype.

TABLE 30.1 General considerations for management of pregnant women with hypertrophic cardiomyopathy.

• Assessment of symptoms and functional status before pregnancy
• Determine degree of left ventricular outflow tract obstruction at rest and with Valsalva maneuver (by echocardiogram) to identify those with severe obstruction
• Risk stratification for sudden cardiac death
• Institute medical therapy for symptomatic patients with β-blockade
• Avoidance of decreases in preload (straining, dehydration, diuretics only if needed)
• Left lateral decubitus position when possible
• Avoid inotropes and vasodilators
• For the hypotensive patient, balance fluids, and vasopressor agents
Postpartum concerns
• Consider treatment of severe anemia
• Monitoring and treatment of pulmonary edema; Medical therapy to optimize loading conditions (treatment of pulmonary edema)
• Hemodynamic and telemetry monitoring for 48–72 h postpartum
• Contraception consideration
• Future consideration of implantable cardioverter defibrillator

Adapted with permission from Stergiopoulos K, Shiang E, Bench T. Pregnancy in patients with pre-existing cardiomyopathies. J Am Coll Cardiol. 2011;58(4):337–50.

Conclusions

HCM is predominantly caused by autosomal dominant mutations, and equal distribution between the sexes would be expected. However, cohort data suggest that men may be more commonly afflicted by HCM. Female patients with HCM had a greater risk of progression to severe congestive heart failure symptoms or death from heart failure over male patients. In comparison to male patients, the more progressive clinical course of HCM in female patients may have been explained in part by the greater prevalence of LV outflow obstruction. Women with HCM presented at more advanced age, with more symptoms and worse cardiopulmonary exercise tolerance. Sex was an important determinant of survival, as women had worse survival in this population. Women commonly have smaller LV cavity dimensions and may be more at risk for development of symptomatic LVOT obstruction, and hence more symptomatic heart failure, than men. Females diagnosed with HCM tended to be older than their male counterparts and were at an increased risk of heart failure and death. Moreover, the enhanced susceptibility of female patients to HCM may lead to other sequelae related to the disease itself, such as AF, stroke, and heart failure. Future sex-specific studies are required to study the disease in the contemporary era on a global level.

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Chapter 31

Dilated cardiomyopathy

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Dilated cardiomyopathy (DCM) is a disease of the myocardium characterized by left ventricular (LV) or biventricular dilatation and systolic impairment in the absence of coronary artery disease or abnormal loading conditions sufficient enough to explain the degree of remodeling [1] (Fig. 31.1). Owing to the heterogeneous origin of the disease, it can manifest in any generation of life and is diagnosed across the globe. In an era when personalized medicine is a major ambition, an understanding of how the disease differs between men and women is vital. Knowledge of sex differences in epidemiology, treatment response, and outcome allows us to identify inequalities in the provision of care, improve the outcomes for those most at risk, and target therapies to those most likely to benefit. Knowledge of disease mechanisms and how these vary between sexes may enable more precise use of available therapies and uncover targets for novel therapies. Our current understanding of this area is limited by a lack of dedicated prospective studies examining these features. Current knowledge largely stems from registries and post hoc analyses of randomized trials. The latter is limited by the relatively small numbers of women enrolled in randomized trials [2]. Over the following chapter, the epidemiology, pathophysiology, treatment, and outcome of DCM will be discussed with a focus on our current understanding of sex-specific differences.

Epidemiology, presentation, and outcome

The prevalence of DCM is debated because of a lack of contemporary epidemiological studies. A cardiomyopathy population screening study performed over 30 years ago in North America using echocardiography estimated the prevalence to be around 1 in 2700 [3]. However, the sensitivity of the technique may have been suboptimal given the limited experience with echocardiography at this time, leading to an underestimation. This is supported by subsequent studies of hypertrophic cardiomyopathy, which have shown the prevalence to be 10-fold greater than the estimates in the initial study [4]. Extrapolating from data on the prevalence of heart failure and the proportion of patients with heart failure and reduced left ventricular ejection fraction (LVEF) who have idiopathic, nonischemic disease, it has been estimated that the prevalence of DCM may be closer to 1 in 400 [5–9]. Nevertheless, it is one of the most common causes of heart failure and remains the most common indication for heart transplantation [10].

As with other forms of heart failure with reduced ejection fraction (HF-REF), the age-adjusted incidence of DCM is higher among men compared with women [11–14]. In a multicentre registry from the United States including 373 patients with new-onset disease, 38% were women with a mean age of 45 years [14]. Similarly, in a registry from the United Kingdom, studying consecutive patients presenting for clinical or imaging evaluation, 33% were women. The median age was similar in both sexes with a median age of 52 years in men and 53 years in women [13]. This is in keeping with data from the Framingham study, suggesting that the risk of developing HF-REF was threefold greater among men compared with women [15].

Similar to the overall HF-REF population, women with DCM typically present with less severe LV systolic impairment, smaller indexed LV cavity size, and a lower prevalence of myocardial fibrosis detected by cardiovascular magnetic resonance, compared with men [13,14,16,17]. Nevertheless, they are more likely to present with symptoms of heart failure, have greater functional impairment, and are more likely to have clinical signs of heart failure, such as pedal edema, raised jugular venous pressure, or a gallop rhythm [13,14,17–20]. This may

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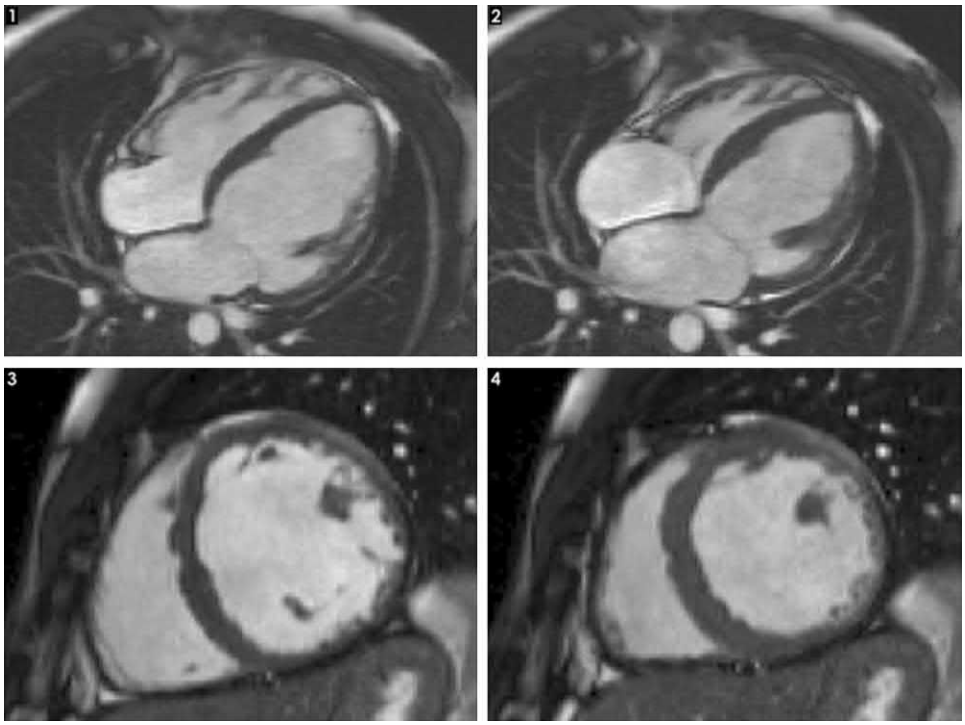

FIGURE 31.1 Cardiovascular magnetic resonance steady-state free precession images of dilated cardiomyopathy. 1: Horizontal long axis image in end diastole; 2: horizontal long axis image in end systole; 3: short axis image at midventricular level in end diastole; 4: short axis image at midventricular level in end systole.

reflect sex differences in cardiac remodeling and a greater propensity to concentric remodeling and diastolic dysfunction among women [21]. It has also been postulated that gender differences in the level of social stressors may contribute to the differences in symptom status [2]. Consistent with this, women with heart failure have worse health-related quality of life and a higher incidence of depression, possibly related to inequalities in caregiver support and healthcare access compared with their male counterparts [17,22,23].

The prevalence of atrial arrhythmia among patients with DCM appears to be higher among men compared with women [17]. One registry study of DCM demonstrated that men were more likely to present with palpitation and had a higher prevalence of atrial fibrillation [13]. Intriguingly, left bundle branch block (LBBB) appears to be more common among women with DCM compared with men and may be associated with a better prognosis in the former [13,17,24,25]. Among patients enrolled across various randomized controlled trials of HF-REF, LBBB was more common among women and RBBB more common in men [17,26,27].

Although the adjusted incidence of DCM is higher in men compared with women, the prevalence of the disease may be more similar [11,12]. This is explained by better survival among women, which persists after adjustment for traditional prognostic indicators and extends across all generations [13,17,20,25]. A post hoc analysis of 7599 patients from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program demonstrated lower adjusted all-cause, cardiovascular, and heart failure mortality among women with HF-REF, with similar results whenever only those with nonischemic disease were analyzed [20]. Similarly, a DCM registry demonstrated lower adjusted mortality among women despite similar use of pharmacological and device therapy among individuals meeting guideline indications [13]. Other analyses have suggested that women may be less likely to receive device therapy or be referred for transplant [2]. Whether this relates to inequalities in care or a greater incidence of reverse remodeling is unclear. Finally, in over 15,000 patients enrolled in clinical trials of HF-REF, women had lower adjusted risk of all-cause mortality, sudden cardiac death, heart failure death, and heart failure hospitalization [17]. The reasons explaining improved outcomes among women are not fully understood. Some potential explanations will be discussed in the Pathology section below.

Etiology

DCM is a common morphological phenotype manifest in a diverse group of individuals because of the combination and interaction of genetic susceptibility and environmental

triggers. While practice has traditionally separated phenotypes based on the presence and type of a perceived trigger, it is increasingly recognized that there is substantial overlap between acquired and genetic forms of the disease (Fig. 31.2). For example, patients labeled as having alcohol-related cardiomyopathy or cardiomyopathy associated with cancer therapy have been shown to have a similar genetic background to those with idiopathic disease [28,29]. It may therefore be better to consider DCM as a common disease occurring in genetically susceptible individuals, which is frequently unmasked by an environmental trigger (Fig. 31.3).

A proportion of individuals may have a primary inflammatory trigger for the disease. This often represents an abnormal innate and acquired immune response to a viral trigger, leading to inflammatory cell infiltration, cytokine release, activation of fibrotic pathways, and myocyte necrosis [30]. It is unclear why certain individuals develop this abnormal response to viral infection; however, genetic susceptibility relating to autosomal recessive mutations has been suggested [31]. Autoimmune processes and toxic injury, such as that secondary to cardiotoxic chemotherapy, have similar effects. DCM in the context of breast cancer chemotherapy represents a specific circumstance in which this phenotype can develop in females [32–34]. Breast cancer is the most common cancer in women, with many therapies known to have cardiotoxic effects [35]. Trastuzumab is a monoclonal antibody directed against the HER2 receptor and is widely used to treat HER2-positive breast cancer. Trastuzumab cardiotoxicity is not dose-dependent and is generally reversible following withdrawal of the agent [34]. Anthracyclines is also used in breast cancer and associated with cardiotoxic effects that can result in LV dysfunction and DCM [32–34]. Anthracycline cardiotoxicity is dose-dependent and, while previously thought to be largely irreversible, it is now clear that LV dysfunction may improve with early detection and heart failure therapy [32–34].

The most common genetic variant associated with DCM is a truncating variant in *TTN* (*TTNtv*), the gene which encodes the largest protein in the human body, titin. Titin spans the length of the sarcomere and acts to regulate and help generate contraction [36]. *TTNtv* have been identified in 25% of cases of familial DCM, 18% of advanced idiopathic DCM, and 10% of ambulatory DCM [37,38]. The same variants may be found in ~1% of healthy controls and among such individuals, it is associated with subclinical remodeling [37,39]. Together with data suggesting that such variants are common in DCM patients exposed to environmental triggers, this has led to the proposal of a "two-hit" hypothesis, whereby the disease is unmasked in individuals with *TTNtv* following an external challenge [28,40]. Consistent with wider cohorts of patients with DCM, it has been demonstrated that,

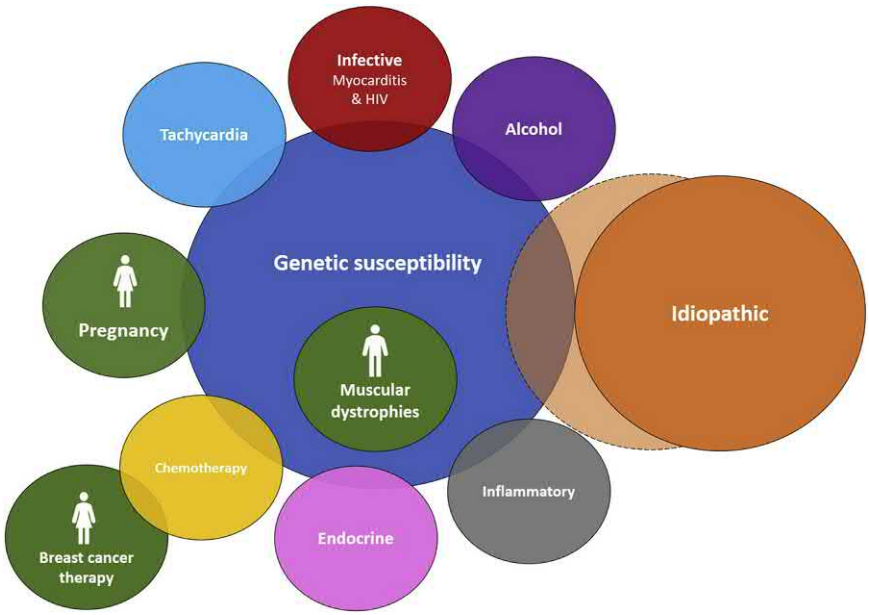

FIGURE 31.2 Etiological contributors to dilated cardiomyopathy phenotype, indicating those with known gender-specific associations. (= associated with female sex; = associated with male sex).

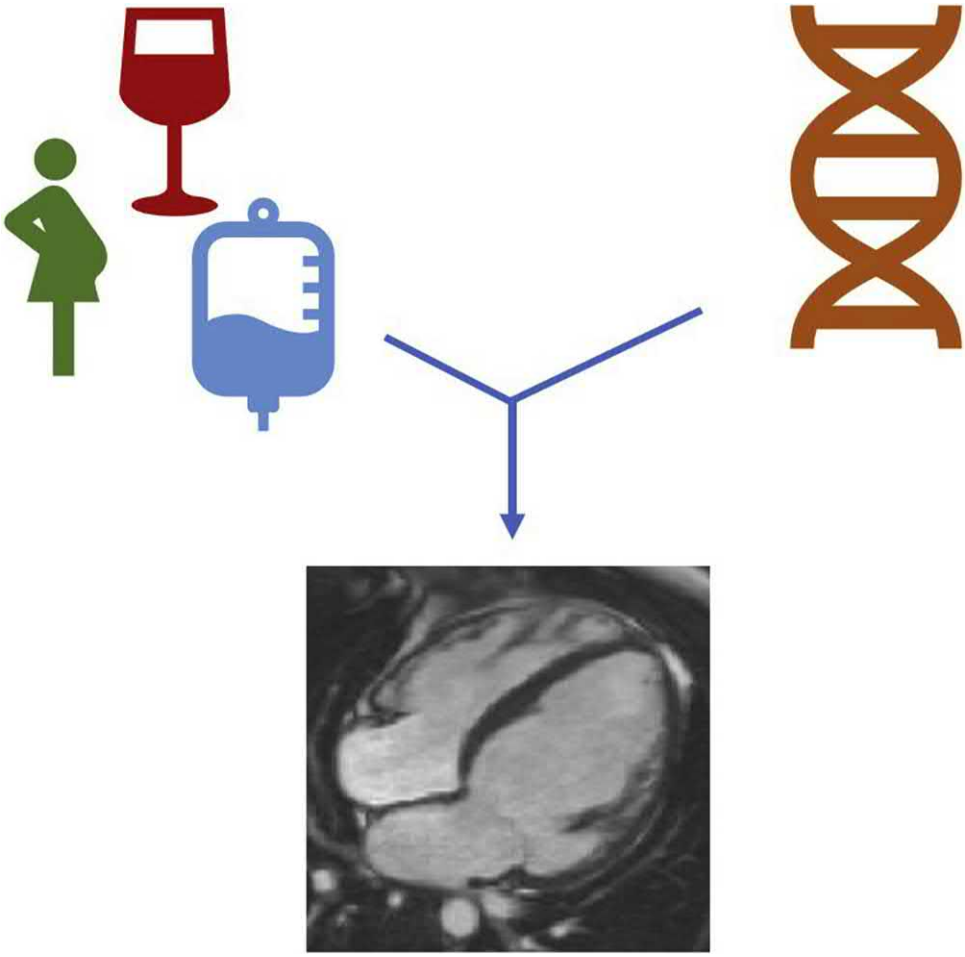

FIGURE 31.3 Two-hit hypothesis. Dialtedcardiomyopathy may often be due to the interaction between an environmental trigger, such as alcohol excess, chemotherapy administration or pregnancy and underlying genetic susceptibility.

among a cohort of patients with *TTNtv,* women had a lower incidence of a composite end-point including death, cardiac transplantation, or LV assist device implantation compared with men, with these events occurring later in life in women [41].

A variant in *LMNA*, the gene encoding lamin AC, a protein in the nuclear envelope, is responsible for around 6% of DCM [1]. This is a penetrant and malignant form of DCM, with almost all carriers developing the phenotype by 50 years of age [42–45]. It is commonly associated with atrioventricular block, ventricular arrhythmia, and recalcitrant heart failure, often leading to sudden cardiac or heart failure death [42–45]. Male sex has been shown to be an independent predictor of adverse arrhythmic events, with an almost threefold greater incidence [42].

X-linked conditions represent a distinct genetic cause of DCM, responsible for a small proportion of overall cases. The dystrophinopathies refer to an overlapping spectrum of X-linked diseases caused by mutations in the dystrophin gene, including Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) [46]. These conditions are characterized by skeletal myopathies and a DCM phenotype. In DMD and BMD, the skeletal muscle manifestations present early in life and are accompanied by significant progressive disability and a high incidence of DCM [46]. Isolated X-linked DCM may also occur without associated skeletal myopathy. As the dystrophinopathies are inherited as X-linked traits, the clinical manifestations are more severe in males than females. Cardiac abnormalities are described in female carriers, including a DCM phenotype, albeit generally less severe and presenting later in life [47]. The phenotype in males is characterized by extensive myocardial fibrosis, most prominent in the subepicardial region of the lateral wall (Fig. 31.4).

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a form of DCM, specific to women. It is defined as an "*idiopathic cardiomyopathy presenting with heart failure secondary to left*

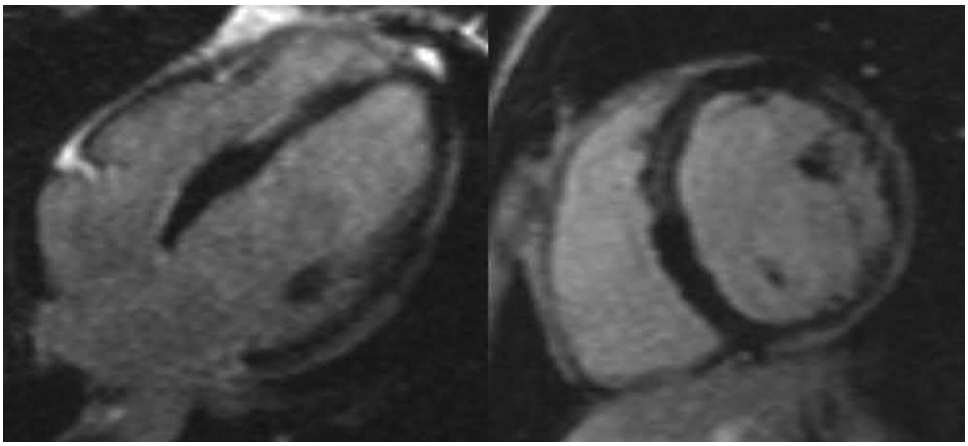

FIGURE 31.4 Late gadolinium enhancement imaging of a patient with dilated cardiomyopathy and Becker's muscular dystrophy. Characteristic subepicardial fibrosis in the lateral wall with mid-wall fibrosis in the septum.

ventricular systolic dysfunction toward the end of pregnancy or in the months following delivery, where no other cause is found" [48]. The incidence varies widely among different countries and ethnicities [49–51]. The incidence in the United States is estimated around 1 in 1000, but may be as high as 1 in 100 in Nigeria and Haiti [49–51]. It is more common among Afro-Caribbean women and is also associated with older age, multiple births, and a previous history hypertension or preeclampsia [52,53].

The geographical differences in the incidence suggest the importance of genetic and/or environmental factors. One study found *TTNtv* in 15% of women with PPCM, which was remarkably similar to patients with idiopathic disease [40]. This again supports a common genetic background that is unmasked by a variety of triggers. Oxidative stress may be this trigger among women with PPCM. Experimental models have demonstrated that this may lead to cleavage of prolactin to form an abnormal 16 KDa fragment [54]. Indeed, suppressing prolactin production using bromocriptine may be effective in the treatment of PPCM [55]. Soluble Flt1 may also play a role in the pathogenesis [56]. It is a hormone secreted by the placenta that is associated with endothelial dysfunction. High levels of the hormone toward the end of pregnancy are associated with PPCM; among women with the condition, levels correlate with outcome [56].

Outcomes with PPCM tend to be favorable compared with idiopathic DCM. The 1-year mortality rate in a US series was only 4%. At the same interval, 72% of women had an LVEF >50% and 52% had an LVEF >55% [57]. The length of time pharmacological therapy needs to be maintained remains unclear. The risk of recurrent heart failure in subsequent pregnancies varies depending on the degree of recovery in cardiac function following the initial episode. If cardiac function recovers completely, the risk of recurrent cardiomyopathy in a subsequent pregnancy appears to be around 25%, with a low risk of mortality [53,58]. If cardiac function fails to recover completely, the risk of recurrent heart failure increases to 50%, with an associated mortality rate as high as 16% [53,58].

Pathology

The histological features of DCM include myocyte hypertrophy, cell death, and interstitial and replacement fibrosis [59] (Fig. 31.5). Myocardial fibrosis is promoted following the activation of the renin–angiotensin–aldosterone and the β-adrenergic axes as part of the heart failure syndrome [60]. It may also occur as a direct result of injurious stimuli, toxins, and genetic variants, which lead to the release of cytokines, such as transforming growth factor-β and reactive oxygen species [60].

Studies of DCM and other cardiovascular conditions have demonstrated a greater expression of extracellular matrix proteins and a higher incidence of myocardial fibrosis among men compared with women [61–64]. The mechanisms explaining these differences remain unclear; however, there is evidence highlighting the role of sex steroid hormones. There is a reduced incidence of cardiovascular disease in premenopausal women compared with men of a similar age, with a sharp increase following the menopause [65]. Preclinical studies have demonstrated that estrogen may prevent cardiomyocyte apoptosis, protect against adenosine triphosphate depletion, reduce reactive oxygen species generation, and counteract processes that drive cardiac hypertrophy [66–69]. Furthermore, estrogen deficiency has been associated with increased histological evidence of interstitial fibrosis [70]. Using an induced pluripotent stem cell model of cardiomyopathy, it has also been demonstrated that estradiol reduces myocyte apoptosis, while testosterone potentiates it [71]. In addition, among patients with arrhythmogenic cardiomyopathy, higher levels of estradiol have been associated with a reduced incidence of adverse events [71]. The effect of sex

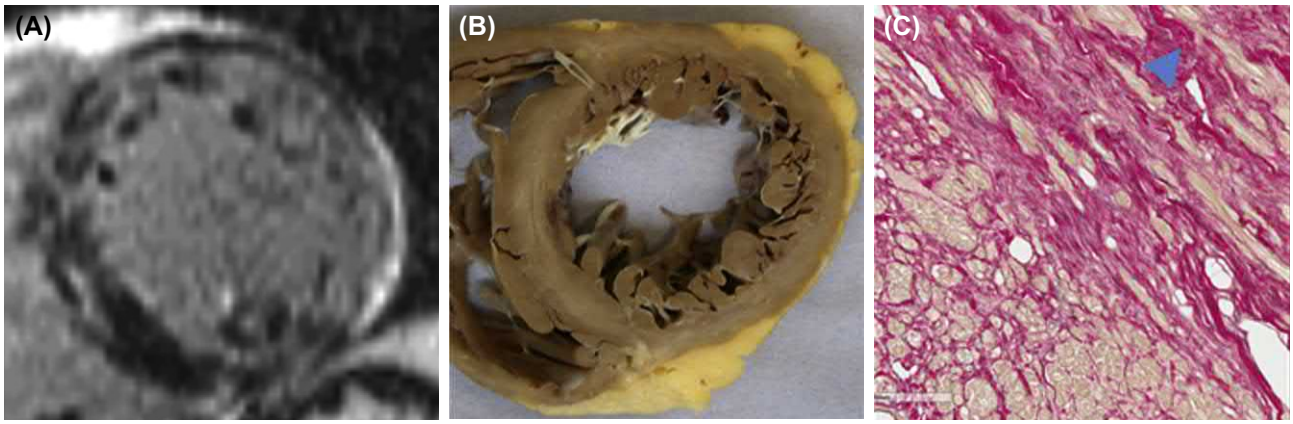

FIGURE 31.5 Myocardial fibrosis in dilated cardiomyopathy. (A) Pretransplant late gadolinium enhancement (LGE) cardiovascular magnetic resonance demonstrating extensive midwall and subepicardial LGE, including the septum at midventricular level. (B) Posttransplant gross examination of a shortaxis slice at midventricular level confirming extensive midwall replacement fibrosis. (C) Posttransplant microscopic examination of a specimen from the septum of the explanted left ventricle at ×300 magnification, confirming replacement (*arrow*) and pericellular fibrosis. *Reproduced with permission from Halliday et al.; PMID: 28351901.*

hormones on myocyte function and survival may help to explain the sex differences in disease phenotype, the prevalence of myocardial fibrosis, and outcome (Fig. 31.6). It is, however, important to note that the lower incidence of DCM among females is also seen in the pediatric population [72]. Given that girls have significantly lower systemic estrogen levels than women, it appears likely that additional unknown factors contribute to the observed sex disparity in DCM incidence. Other studies have also demonstrated sex differences in gene expression among DCM patients [73]. Further studies designed to prospectively investigate sex-specific differences in disease mechanisms are needed to enable the harnessing of this information for the development of novel therapeutics (Fig. 31.7).

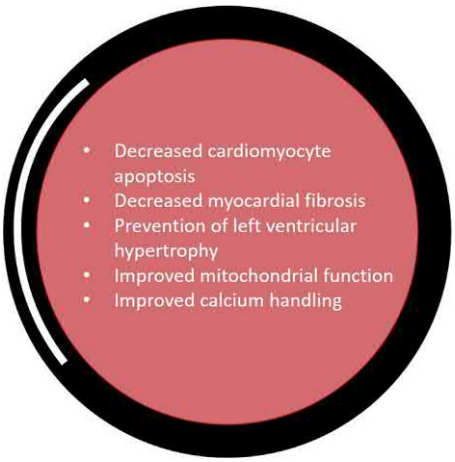

FIGURE 31.6 Potential effects of estrogens on arrhythmogenic cellular processes.

Pharmacological and device therapy

Pharmacological and device therapy is used in DCM in line with wider guidelines for the treatment of HF-REF [74]. While precision therapeutics targeting the underlying disease mechanisms is a long-term ambition, the mainstay of current management treats the heart failure syndrome that results from contractile impairment. The benefit of angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers, β-blockers, and mineralocorticoid receptor antagonists for patients with an LVEF<40% is proven in large-scale randomized trials [75–84]. Evidence is emerging that patients with midrange ejection fraction (LVEF 40%–50%) may also benefit from such treatments [85]. The use of the angiotensin receptor/neprilysin inhibitor, sacubitril/valsartan is now recommended among patients if symptoms persist despite triple therapy [8,74], while ivabradine provides benefit if patients are in sinus rhythm with a heart rate >70 beats per minute [86]. Implantable cardioverter defibrillators (ICDs) are recommended for patients with heart failure symptoms and an LVEF<35%, who have a life expectancy greater than 1 year and have been on pharmacological therapy for at least 3 months (Table 31.1) [74]. The recent Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure (DANISH) trial has, however, cast doubt on the benefit of ICDs in nonischemic disease, failing to demonstrate a mortality reduction in this group despite reducing the incidence of sudden cardiac death [9]. It has been suggested that more accurate and precise ways of identifying patients who are most likely to benefit from ICD therapy are required, taking into account both the risk of sudden cardiac death and the competing risks of nonsudden death [87]. Cardiac resynchronization therapy is recommended for patients with an LVEF<35% and a QRS

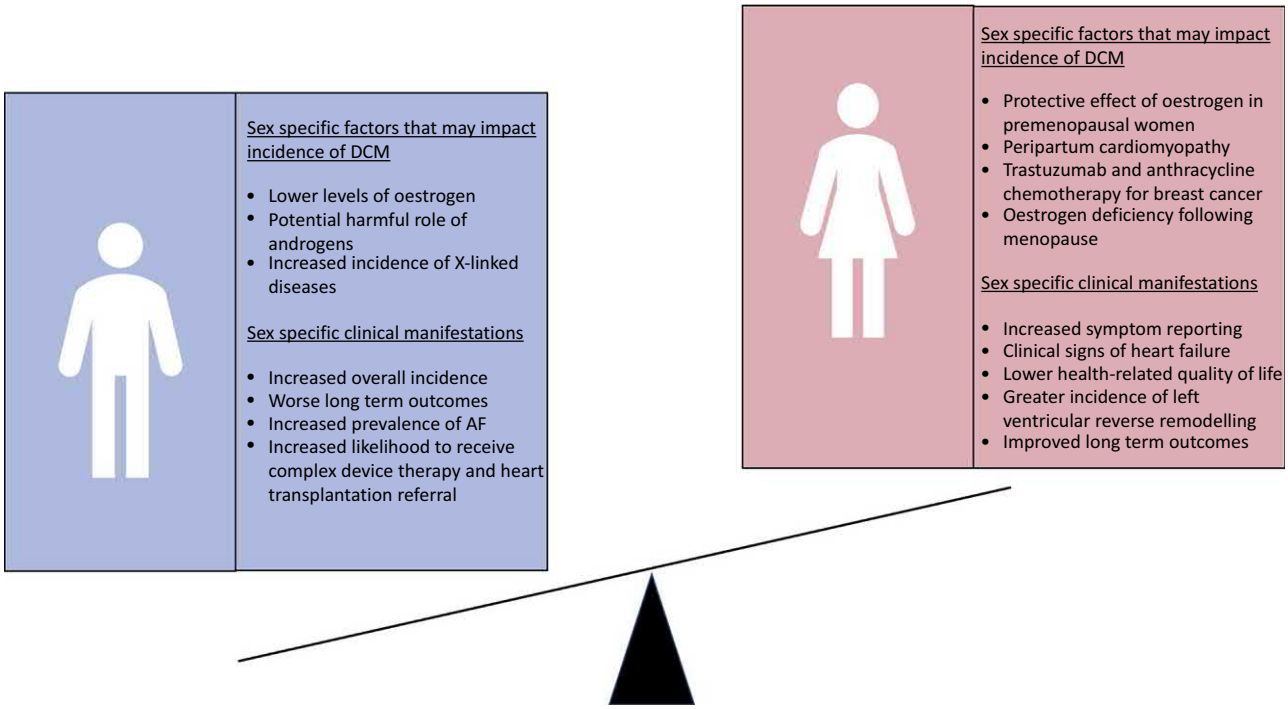

FIGURE 31.7 Sex-specific factors and clinical manifestations in dilated cardiomyopathy (DCM).

duration >150 ms [74]. The incidence of reverse remodeling with CRT is higher among patients with DCM compared with those with ischemic heart disease [88].

Sex differences in treatment response are not fully understood because of the small number of women enrolled in randomized trials. Metaanalyses of trials investigating ACEi in HF-REF have suggested comparable effects of these agents on mortality and hospitalization in women and men [89]. Analyses of landmark trials investigating β-blockers, mineralocorticoid receptor antagonist, and sacubitril/valsartan also suggest that these treatments have comparable effects among men and women [8,83,90,91].

Whether or not there are differences in the effect of ICDs on outcome between men and women with DCM is debated. As with other treatments, a lack of dedicated studies and the small number of women enrolled in large-scale device trials make it difficult to draw definitive conclusions. The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study evaluated ICD implantation in patients with DCM, an LVEF ≤35%, and nonsustained ventricular arrhythmia [92]. A reduction in SCD was observed; however, all-cause mortality was not different with ICD therapy. In post hoc subgroup analysis, a reduction in mortality was seen among men but not among women. However, in further analysis, there was no interaction between sex and the effect of ICD implantation on mortality [93]. Similar trends toward sex differences in the benefit from ICDs have been observed in other landmark trials; however, post hoc interaction tests have also been negative [9,94,95]. This supports the need for sex-specific trials which are prospectively powered to deal with this issue.

Sex-specific differences in the response to CRT have also been debated. Women receiving CRT have been shown to have reduced mortality and a greater incidence of LV reverse remodeling compared with men [25]. The difference in mortality appears to be primarily driven by those with LBBB, which is more frequent among women [25]. A large individual patient data metaanalysis of CRT trials has, however, demonstrated no difference in the effect of CRT on mortality or a composite of all-cause mortality and heart failure hospitalization between sexes [96]. This suggests that the difference in mortality may not be driven by sex-specific differences in treatment response, but rather differences in the natural history of the disease. Another analysis of patients with mild heart failure suggested that women may get benefit from CRT at shorter QRS durations compared with men [26]. It has been suggested that this may be related to differences in height between sexes; shorter patients with smaller left ventricles may be more likely to gain benefit at shorter QRS durations [27]. Supporting this concept, one analysis demonstrated that sex and height were independent predictors of a composite of mortality and heart failure hospitalization among patients receiving CRT, while sex was not [27].

TABLE 31.1 Implantable cardioverter defibrillators for primary prevention purposes in dilated cardiomyopathy.

Study	N	Inclusion criteria	Intervention	Follow-up (median)	All-cause mortality	Post hoc subgroup analysis based on sex	SCD
SCDHeFT [95] (DCM cohort)	1211	LVEF<35% NYHA 2−3	ICD versus OMT versus amio	46 months	I: 21.4%, C: 27.9% (5 yrs) HR 0.73; 95% CI 0.50 −1.07 $P = .06$	W: HR 0.96; 95% CI: 0.58 −1.61 M: HR 0.73; 95% CI: 0.57 −0.93	
DEFINITE [93,94]	458	LVEF<36% NYHA 1−3 NSVT or PVCs	ICD versus OMT	29 months	I: 12.2%, C: 17.4% HR 0.65; 95% CI 0.40 −1.06 $P = .08$	W: HR 1.14; 95% CI: 0.50 −2.64 M: HR 0.49; 95% CI: 0.27 −0.90	I: 1.3%, C:6.1% HR 0.20; 95% CI 0.06 −0.71 $P = .006$
DANISH [9]	1116	LVEF<35% NYHA 2−3 (4 if CRT) NT-pro-BNP>200 pg/mL	ICD versus OMT	68 months	I: 21.6%, C: 23.4% HR 0.87; 95% CI 0.68 −1.12 $P = .28$	W: HR 1.03; 95% CI: 0.57 −1.87 M: HR 0.85; 95% CI: 0.64 −1.12	I: 4.3%, C: 8.2% HR 0.50; 95% CI 0.31 −0.82 $P = .005$

amio, amiodarone; *C*, optimal medical therapy arm; *CI*, confidence interval; *CRT*, cardiac resynchronization therapy; *DCM*, dilated cardiomyopathy; *HR*, hazard ratio; *I*, implantable cardioverter defibrillator therapy arm; *ICD*, implantable cardioverter defibrillator; *LVEF*, left ventricular ejection fraction; *M*, men; *NYHA*, New York Heart Association; *NT-pro-BNP*, N-terminal-pro−peptide brain natriuretic peptide; *NSVT*, nonsustained ventricular tachycardia; *OMT*, optimal medical therapy; *PVCs*, premature ventricular complexes; *SCD*, sudden cardiac death; *W*, women.
Adapted from Halliday BP, Cleland JGF, Goldberger JJ, Prasad SK. Personalizing risk stratification for sudden death in dilated cardiomyopathy: the past, present, and future. Circulation 2017;136:215−31; with permission.

Conclusion

In conclusion, DCM appears to present around twice as often in men compared with women and is associated with worse outcomes in the former. While important sex differences in disease mechanisms and treatment response are likely to exist, a lack of dedicated and prospective studies examining these features currently limit our understanding. As we move into the era of personalized medicine, more in-depth study of these concepts may allow us to tailor available treatment more appropriately and discover novel therapeutics with the aim of improving outcomes and quality of life.

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Chapter 32

Arrhythmogenic right ventricular cardiomyopathy

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Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy associated with pathogenic variants (mutations) in genes encoding the cardiac desmosome. Patients with ARVC have progressive fibrofatty replacement of the ventricular myocardium, frequent ventricular arrhythmias, typically predominant right ventricular dysfunction, and a substantial risk of sudden cardiac death [1]. While relatively rare (prevalence 1/2500−1/5000), ARVC is an important cause of sudden cardiac death in young individuals and athletes [2]. There is substantial clinical heterogeneity in the outcomes of both patients and at-risk family members [3]. Considerable research has focused on identifying demographic, clinical, genetic, and environmental predictors of patient outcomes. In this chapter, we describe how patient sex is associated with clinical outcomes and describe emerging evidence of possible mechanisms for these associations.

Diagnosis

ARVC is diagnosed based on the 2010 Task Force Criteria [4] which integrate cardiac and genetic testing results with family and clinical history. Table 32.1 presents this diagnostic algorithm in the form of a checklist. Major and minor criteria are assigned for repolarization abnormalities, depolarization abnormalities, right ventricular enlargement and dysfunction, fibrofatty replacement on cardiac biopsy, ventricular arrhythmias, family history of ARVC or sudden cardiac death, and genotype. A definite ARVC diagnosis is established when a patient meets at least two major, one major and two minor, or four minor criteria from different categories. Diagnostic criteria for male and female patients are identical with the exception of sex-specific cutoffs for indexed right ventricular size necessary to meet a major or minor criterion on cardiac magnetic resonance imaging. The criteria successfully diagnose family members with early disease before emergence of substantial arrhythmic risk [5,6]. However, the 2010 criteria are acknowledged to not be sufficiently sensitive for patients with a biventricular or left-predominant presentation and updates to the criteria are being considered.

Natural history

ARVC patients typically present between adolescence and midadulthood (average 35.1 ± 14.9 years) with symptoms associated with ventricular arrhythmias including palpitations, syncope, sudden cardiac arrest, or sudden death [3]. Natural history of the largest ARVC cohort to date is shown in Fig. 32.1. In this series of >1000 ARVC patients and family members [3], 95% of 439 ARVC probands (64% male) were symptomatic at diagnosis with more than half (56%) presenting with sustained ventricular tachycardia (VT) and an additional 11% with sudden cardiac death or resuscitated arrest. Arrhythmias frequently are associated with exercise. Family members benefit from cascade screening and are often asymptomatic at diagnosis [3].

Male patients on an average have a younger age of onset and are more frequently the family proband in gene-positive families [7]. Males also more frequently have an onset of ARVC during adolescence [8]. This is important as adolescents are most likely to present with sudden cardiac death [7]. At the other end of the age spectrum, Bhonsale et al. [9] showed that one-fifth of ARVC patients in a US/Dutch cohort presented at age 50 or older and 3% were diagnosed after age 65. Among this group there was again male predominance (61% male) and these older male patients had worse arrhythmic outcomes in comparison with women diagnosed at an older age.

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TABLE 32.1 2010 Task Force Criteria for Diagnosis of ARVC (Checklist)

Definite = 2 major OR 1 major + 2 minor / Borderline = 1 major + 1 minor OR 3 minor / Possible = 1 major OR 2 minor

	I. Global/regional dysfunction/structural alterations		II. Tissue characterization of wall
Major		**Major**	
	By 2D Echo		• Residual myocytes < 60% by morphometric analysis (or <50% if estimated), w/fibrosis replacement of RV free wall myocardium in ≥1 sample, w/ or w/o fatty replacement of tissue on endomyocardial biopsy
	• Regional RV akinesis, dyskinesia, or aneurysm		
	• *and* 1 of the following (end diastole):		
	____PLAX RVOT ≥32 mm (correct for body size [PLAX/BSA] ≥19 mm/m^2)	**Minor**	
	____PSAX RVOT ≥36 mm (correct for body size [PSAX/BSA] ≥21 mm/m^2)		• Residual myocytes 60% to 75% by morphometric analysis (or 50% to 60% if est.) w/fibrous replacement of the RV free wall in ≥1 sample, w/ or w/o fatty replacement of tissue on endomyocardial biopsy
	____or fractional area change ≤33%		
	By MRI:		
	• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction		**III. Repolarization abnormalities**
	• *and* 1 of the following :	**Major**	• TWI (V_1, V_2, V_3) or beyond; >14 yrs; in absence of complete RBBB QRS ≥120 ms
	____Ratio of RV end-diast vol to BSA ≥110 mL/m^2 (**male**) or ≥100 mL/m^2 (**female**)		
	____or RV ejection fraction ≤40%	**Minor**	• TWI in V_1 and V_2; >14 yrs; in absence of complete RBBB or in V_4, V_5, or V_6
	By RV Angiography:		• TWI in V_1–V_4; >14 yrs; in presence of complete RBBB
	• Regional RV akinesia, dyskinesia, or aneurysm		
			IV. Depolarization/conduction abnormalities
Minor		**Major**	• Epsilon wave (reproducible low-amp signals between end of QRS complex to onset of T wave) in right precordial leads (V_1–V_3)
	By 2D Echo:		
	• Regional RV akinesia or dyskinesia		
	• *and* 1 of the following (end diastole):	**Minor**	• LP by SAECG in ≥1 of 3 parameters in absence of QRS duration of ≥110ms on ECG
	___PLAX RVOT ≥29 to <32 mm (correct body size PLAX/BSA ≥16 to <19 mm/m^2)		___ Filtered QRS duration (fQRS) ≥114ms
	___PSAX RVOT ≥32 to <36 mm (correct body size [PSAX/BSA] ≥18 to <21 mm/m^2)		___ Duration of terminal QRS <40μV (LAS duration) ≥38ms
	___or fractional area change >33% to ≤40%		___ RMS voltage of terminal 40 ms ≤20μV
	By MRI:		• TAD of QRS ≥55ms measured from nadir of S wave to end of QRS, including R′, in V_1, V_2, or V_3, in absence of complete RBBB
	• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction		
	• *and* 1 of the following:		
	___Ratio of RVEDV to BSA ≥100 to <110mL/m^2 (**male**) or ≥90 to <100mL/m^2 (**female**)		
	___or RV EF >40% to ≤45%		

Continued

TABLE 32.1 2010 Task Force Criteria for Diagnosis of ARVC (Checklist)—cont'd

Definite = 2 major OR 1 major + 2 minor / Borderline = 1 major + 1 minor OR 3 minor / Possible = 1 major OR 2 minor

	V. Arrhythmias			VI. Family history
Major	• LBS NSVT or sustained VT (neg or indet QRS in II, III, and aVF and pos in aVL)		**Major**	• ARVC/D confirmed in FDR who meets TFC
				• ARVC/D confirmed pathologically at autopsy or surgery in FDR
Minor	• NSVT or sustained VT of RV outflow configuration, LBI (pos QRS in II, III, and a VF and neg in aVL) or of unknown axis			• Pathogenic mutation (assoc or probably assoc w/ ARVC/D) in pt under eval
	• >500 ventricular extrasystoles per 24 hours (Holter)			
			Minor	• Hx of ARVC in FDR in whom not poss or pract to determine if FM meets TFC
				• Premature SD (<35 yrs) due to suspected ARVC/D in FDR
				• ARVC/D confirmed pathologically or by current TFC in second DR

Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Sanborn DM, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation. 2010 Apr 6;121(13):1533-41.

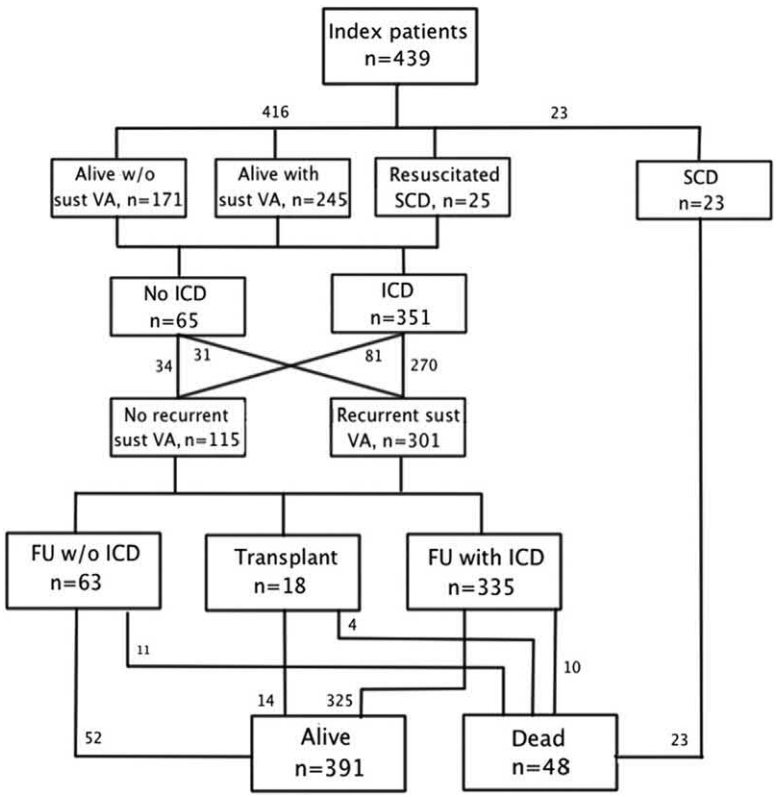

FIGURE 32.1 Schematic representation of natural history of ARVC index patients. The majority of patients present with VA; however, survival after implantation of an ICD is good. *ARVC*, arrhythmogenic right ventricular cardiomyopathy; *ICD*, implantable cardioverter defibrillator; *VA*, ventricular arrhythmia; *w/o*, without. *From Groeneweg, Bhonsale, James, te Riele, Dooijes, Tichnell et al. Clinical presentation, long-term follow-up, and outcomes of 1001 arrhythmogenic right ventricular dysplasia/cardiomyopathy patients and family members. Circ Cardiovasc Genet June 1, 2015; 8(3):437–446, by permission of American Heart Association.*

ARVC has a highly arrhythmic course. A recent meta-analysis including 28 studies of definite ARVC patients showed an average prevalence of sustained ventricular arrhythmias of 10.6% per year (range 3.0%–30.1%) [10]. Management therefore frequently involves placement of implantable cardioverter defibrillators (ICDs) to prevent sudden cardiac death [11]. ARVC patients also experience progressive right and left ventricular dysfunction and enlargement with a generally slow but variable rate of change [12,13]. In most ARVC cohorts, heart failure is reported in only a minority of patients (4%–16%) [14,15]. However, a recent study focused on defining prevalence of signs and symptoms of both left- and right-sided heart failure showed that 49% of ARVC patients met criteria for clinical heart failure [16]. This suggests that heart failure symptoms may be underrecognized in ARVC or possibly that a new phase in the natural history of ARVC is being described as improved arrhythmia management and widespread access to ICDs for high-risk patients improves survival from life-threatening arrhythmias earlier in the disease course. Nonetheless, should sudden cardiac death be prevented, most ARVC patients have a favorable prognosis. Annual mortality is reported between 1% and 2% in recent cohorts [3,17–19].

Genotype

ARVC is often called a disease of the desmosome [20]. Cardiac desmosomes are adhesion junctions composed of a symmetrical group of proteins (cadherins, armadillo proteins, and plakins). Pathogenic variants (e.g., mutations) in the desmosomal genes (*PKP2*, *DSP*, *DSC2*, *DSG2*, and *JUP*) can be detected in approximately half of ARVC probands and up to two-thirds of ARVC patients [3]. Inheritance is considered autosomal dominant with reduced, age-related penetrance and highly variable expressivity. Autosomal recessive forms of ARVC are well-recognized. Indeed, the first desmosomal ARVC gene identified (*JUP*, encoding plakoglobin) was for Naxos disease, a rare cardiocutaneous autosomal recessive form of ARVC [21]. As shown in Table 32.2, pathogenic variants in nondesmosomal genes have been identified in a minority of patients. Some genes have as-yet limited evidence for their association with ARVC and are awaiting confirmation in other cohorts. This group includes two recently identified genes encoding proteins of the area composita, *CTNNA3* [22] and *CDH2* [23]. Other genes have well-established associations with other cardiomyopathies and arrhythmia syndromes and likely reflect genetic heterogeneity of these disorders.

Knowledge of genotype can inform clinical management. For instance, increased likelihood of left ventricular involvement and heart failure is associated with *PLN* [24] and *DSP* variants [7,25]. In addition, patients with multiple pathogenic variants have worse clinical outcomes [7,26]. Importantly, identification of one or more pathogenic variants in a family allows for cascade genetic screening of family members facilitating evidence-directed cardiac screening and early disease detection. Thus, genetic testing for ARVC is a class I recommendation [27].

Clinical variability

Genotype does not fully, or even primarily, explain the wide variability in clinical outcomes of either individuals with pathogenic ARVC-associated variants or of ARVC patients. Even within the same family, individuals with the same pathogenic ARVC-associated variant will have very different outcomes (variable expressivity) with penetrance in most cohorts less than 50% [28]. After diagnosis, patient outcomes vary widely as well. Identifying clinical, demographic, and environmental predictors of penetrance and clinical outcomes has thus been a substantial focus of both clinical and translational research over the past decade [10]. The next section of this chapter describes the evidence for the association of sex with clinical outcomes and discusses possible mechanistic explanations including exercise, hormones, and inflammation.

Sex differences in arrhythmogenic right ventricular cardiomyopathy

Observations regarding sex differences in arrhythmogenic right ventricular cardiomyopathy

As ARVC has an autosomal dominant inheritance pattern, one would expect that equal numbers of males and females are affected. However, sex differences in the prevalence, phenotypic manifestations, and clinical course of ARVC patients have been described. In addition, significant differences in psychosocial and quality of life outcomes have been reported between male and female ARVC patients.

Prevalence and phenotypic manifestations

Since its first comprehensive description in 1982 [29], ARVC (at the time known as “right ventricular dysplasia”) was thought to have a male predominance with an estimated ratio of 3:1 [30–32]. An early Italian report showed that approximately two-thirds of 42 ARVC patients were male (64% vs. 36%) [33], which was confirmed by a Dutch study revealing a male predominance of approximately 71% males versus 29% females among 149 ARVC index patients [31]. Bauce et al. [30] were the first to perform a comprehensive analysis on sex differences in ARVC. The authors evaluated 171 definite ARVC patients (71% men) using medical history, ECG, 24-h Holter monitoring, signal-averaged ECG, and echocardiography. They observed that male ARVC patients had a higher prevalence of abnormal ECG and late potentials than female patients. In addition, males with ARVC had larger right ventricular dimensions and more frequent left ventricular involvement. While this did not translate to a more severe arrhythmic phenotype in this cohort, these results point toward a more severe phenotype in male ARVC patients.

TABLE 32.2 Genetic architecture of ACM.

Gene	Protein	Prevalence in ACM	Excess in cases	Phenotype
Desmosomal				
PKP2	Plakophilin-2	20–46%		Classic ARVC, typically right dominant
DSP	Desmoplakin	3–15%	3–15%	Heterozygous variants—ARVC, frequent biventricular involvement; also causes dilated cardiomyopathy. Rare homozygous variants—Carvajal syndrome (cardiocutaneous)
DSG2	Desmoglein–2	3–20%	3–20%	ARVC, frequently biventricular; also causes dilated cardiomyopathy
DSC2	Desmocollin–2	1–15%	1–15%	ARVC
JUP	Plakoglobin	0–1% (Naxos, Greece)	0–1% (Naxos, Greece)	Naxos disease (cardiocutaneous). Autosomal recessive
Founder variants				
PLN	Phospholamban	0–4% (30% in Dutch population)	0–4% (30% in Dutch population)	ARVC, frequently biventricular, older age of onset. Dutch founder mutation most common. Worse outcomes in females. Also causes dilated cardiomyopathy. Several other variants identified
TMEM43	Transmembrane protein 43	0–2% (frequent in Newfoundland, Canada)	0–2% (frequent in Newfoundland, Canada)	ARVC, highly lethal ventricular arrhythmias in males. Younger male onset. Canadian (Newfoundland) founder mutation
Other/overlap syndromes				
SCN5A	$Na_V1.5$	2%	2%	ARVC. Also causes Brugada syndrome, dilated cardiomyopathy, long QT syndrome
LMNA	Lamin A/C	0–4%	0–4%	Overlap with dilated cardiomyopathy
TTN	Titin	0–10%	0–10%	Overlap with dilated cardiomyopathy
FLNC	Filamin C	0–3%	0–3%	Arrhythmogenic cardiomyopathy with left-sided predominance, ARVC has been reported
Emerging genes				
CTNNA3	Alpha-T catenin	0–2%	0–2%	ARVC—few cases reported
CDH2	Cadherin-2	0–2%	0–2%	ARVC—few cases reported
TJP1	Tight junction protein 1	0–4%	0–4%	ARVC—few cases reported

Of note, the literature on sex differences in ARVC is not uniform and regional disparities have been reported. In general, European studies report a male predominance [30,31,33], whereas North American cohorts report a similar prevalence between the sexes [3,6,34]. More specifically, among individuals enrolled in the North American ARVC Registry, there were no differences in presentation (i.e., age at first symptom and overall presentation), clinical characteristics (i.e., number of major or minor diagnostic criteria), and disease severity (i.e., occurrence of arrhythmic events) among 70 male and 55 female patients [34]. A conclusive explanation for these geographic differences is lacking. One possible explanation may be regional differences in exercise participation between the sexes (see below) or different genetic background: for example, ARVC patients with a *TMEM43* founder variant (ARVD5) are overwhelmingly male [35,36], whereas ARVC patients carrying a mutation in the nondesmosomal phospholamban (*PLN*) gene have a slight female predominance [37]. In this context, interesting data were obtained by Rigato et al., who showed that the genotype–phenotype association is importantly modulated by sex: in their study, ARVC prognosis was worse in males with pathogenic desmosomal variants, and men with multiple variants exhibited the highest cumulative risk of arrhythmias [26].

Disease course and outcomes

In contrast with the conflicting data on sex-related differences in ARVC prevalence, the observed effect of sex on arrhythmic occurrence is more uniform [6,32,34,38,39]. This was recently evaluated by Lin et al., who showed that among 70 unselected ARVC patients followed over almost 3 years, the majority of patients experiencing ventricular arrhythmias were male (Fig. 32.2) [32]. Bosman et al. [10] subsequently summarized the literature on arrhythmic outcomes in ARVC, which is graphically represented in Fig. 32.3. In 22 of 28 evaluated studies, the authors observed that male sex was associated with a higher risk of ventricular arrhythmias. A metaanalysis of 617 definite ARVC patients from seven studies confirmed a higher arrhythmic risk in males (HR 1.83, $P < .001$). Even in the North American ARVC Registry study, in which overall arrhythmic occurrence was similar between the sexes, rapid ventricular arrhythmias and death were more often observed in men [34]. More conclusive evidence confirming a higher arrhythmic risk in males came from a recent study in 528 primary prevention ARVC patients from five registries in North America and Europe [40]. In their analyses, male sex had a strong univariable association with sustained ventricular arrhythmias, which remained significant after correction for all other six risk factors (multivariable HR 1.63, $P = .005$).

Regarding heart failure and transplantation outcomes, insufficient data are available to draw any definite conclusions on sex-based differences. In a large study comprising 289 ARVC patients, female sex was independently associated with heart failure ($P = .01$) [16], whereas another study in 171 patients showed no difference in heart failure outcomes ($P = .09$) [30]. The majority (61%) of 18 cardiac transplantation recipients in yet another report were males, although some of these men received a transplant because of intractable arrhythmias [41]. Future collaborative studies combining data from multiple registries may shed light on the effect of sex on heart failure and cardiac transplantation in ARVC.

Psychosocial and quality of life outcomes

ARVC patients experience high levels of generalized, cardiac, and ICD-related anxiety [42]. A study of adults with ARVC who had ICDs implanted showed clinically significant anxiety in 40% of patients and ICD-related anxiety substantially higher than in other cardiac populations. In this study, clinically significant anxiety was independently associated with younger age, recent ICD implantation, poorer functional capacity, and history of ICD shock. There was no difference in frequency of clinically significant anxiety in male and female patients. In contrast, in a follow-up study of 159 patients [43], women reported significantly higher ICD-specific shock anxiety and lower mental quality of life compared with their male counterparts. Overall, ARVC patients had reduced physical and mental quality of life compared with the general population.

Like others living with or at risk for inherited cardiomyopathies, ARVC patients and at-risk family members also frequently have experienced losses in the family [1,44]. Sudden cardiac death events which are associated with prolonged grief and posttraumatic stress symptoms are common presenting symptoms in ARVC [44,45]. In a study of 103 adult first-degree relatives of sudden cardiac death victims with a suspected genetic cause, 20% had prolonged grief and nearly half posttraumatic stress symptoms [46]. Both prolonged grief and posttraumatic stress were particularly likely among mothers and witnesses of the event.

Both the frequent adjustment difficulties and psychological distress in ARVC patients and the challenges associated with sudden cardiac death histories highlight the importance of a multidisciplinary team being available to care for these complex families [27].

Possible mechanisms underlying sex differences in arrhythmogenic right ventricular cardiomyopathy

Sex hormones

Signs and symptoms of ARVC are typically delayed to adolescence and young adulthood, with a peak at the age of 15–30 years [6,7]. As such, it seems reasonable to think that sex hormones play an important role in the development of the arrhythmogenic substrate in ARVC. Indeed, several studies have shown that cardiac remodeling, including fibrosis, hypertrophy, lipogenesis, and apoptosis, is associated with the interrelationship between estrogen and testosterone (summarized in Refs. [47,48]). Animal studies have shown that the response to volume- or pressure-induced cardiomyocyte stress is different in male and female hearts: females show more hypertrophy, less fibrosis, and a preserved ejection fraction compared with males [47,49,50]. In addition, different mouse models have shown that estrogen is involved in calcium handling and metabolism of glucose and fatty acids [51]. This is especially interesting for the setting of *PLN* and *PKP2* variants, as both increase calcium load and hence produce an arrhythmogenic substrate [52].

Recently, Akdis et al. performed a seminal study investigating the role of sex hormones in ARVC [53]. The authors measured five sex hormones in 54 ARVC patients (72% males), among whom 26 experienced a major adverse clinical event (MACE; including VT, ventricular fibrillation

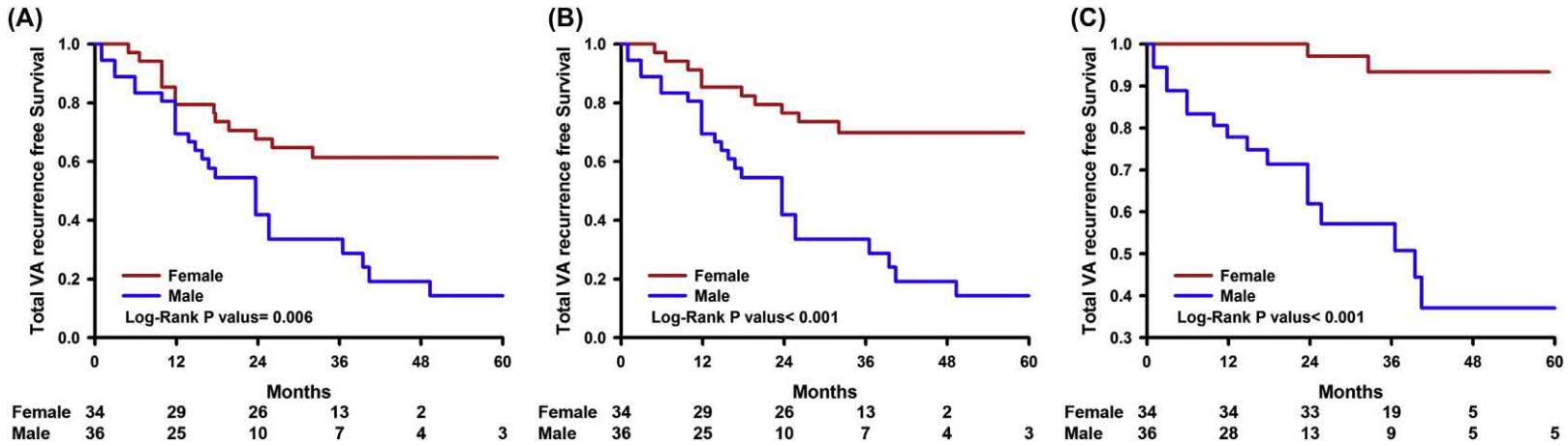

FIGURE 32.2 Ventricular arrhythmia free survival in 36 male versus 34 female ARVC patients during 37.5 ± 17.0 months of follow-up. (A) Any ventricular arrhythmia recurrence; (B) sustained VT/VF recurrence; (C) nonsustained VT recurrence. *ARVC*, arrhythmogenic right ventricular cardiomyopathy; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia. *From Lin, Chung, Lin, Chang, Lo, Hu, Tuan, Chao, Liao, Chang, Chen, Walia, Te, Yamada, Chen et al. Gender differences in patients with arrhythmogenic right ventricular dysplasia/ cardiomyopathy: clinical manifestations, electrophysiological properties, substrate characteristics, and prognosis of radiofrequency catheter ablation. Int J Cardiol 2017;227:930–937, by permission of Elsevier.*

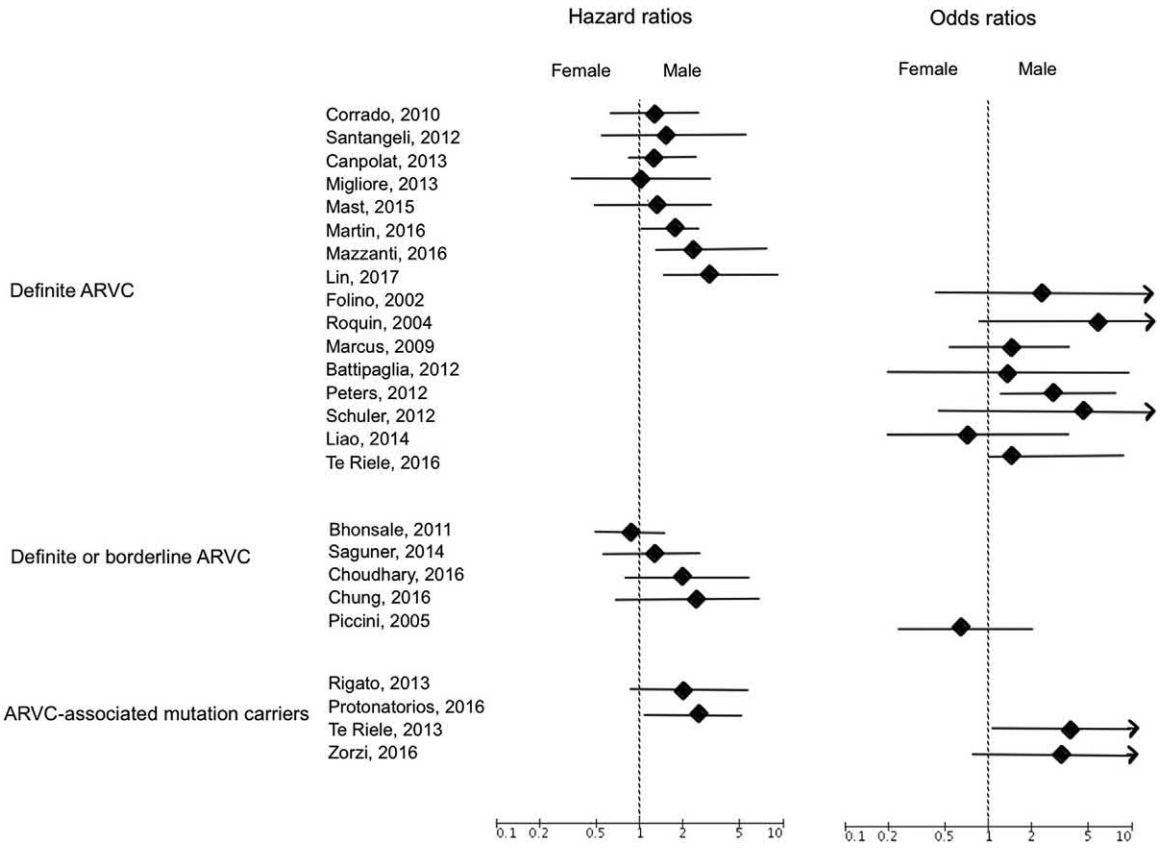

FIGURE 32.3 Overview of the literature on sex differences in arrhythmic risk in arrhythmogenic right ventricular cardiomyopathy (ARVC). Univariable hazard ratios (left) and odds ratios (right) for the risk of sustained ventricular arrhythmias are shown. Overall, a tendency of increased risk is observed in males, although statistical significance was only reached in seven (28%) of studies.

[VF], and arrhythmic syncope). Total and free testosterone levels were independently associated with MACE in males, whereas estradiol was significantly decreased in females with arrhythmic outcomes. These clinical findings are supported by in vitro studies: an induced pluripotent stem cell–derived cardiomyocyte model with a plakophilin-2 mutation revealed that at clinically relevant concentrations, testosterone worsened and estradiol improved cardiomyocyte apoptosis and lipogenesis [53]. As such, sex hormones may play a role in ARVC pathogenesis and (at least in part) explain why females have a less severe disease phenotype and fewer arrhythmic events as compared with male ARVC patients.

Physical activity and behavioral differences

Behavioral differences between the sexes (i.e., gender) may also play a role in the clinical heterogeneity of ARVC. Gender-sensitive lifestyle choices, such as exercise participation and nutritional habits, are known to differ between females and males [30]. For ARVC, this is especially interesting, as high-intensity physical exercise has an important role in age-related penetrance [8,54] and occurrence of adverse events [18,54–57]. While this effect of physical activity on disease pathogenesis is already present in desmosomal mutation carriers [58], it disproportionally affects nondesmosomal (i.e., "gene-elusive") ARVC cases [59], in whom restriction of exercise conferred the greatest reduction of arrhythmic events [55]. As physical exercise is known to trigger testosterone release [60–62] and the intensity of exercise participation is different between males and females [30], this gender difference may modify the relationship between biological sex and ARVC development. However, objective data on the modifying effect of exercise and other behaviors (e.g., alcohol use and smoking) on disease expression in female versus male patients are unfortunately lacking.

Impact on management and screening recommendations

Family screening

Several studies have reported that approximately one in three at-risk relatives develop ARVC: penetrance was 34% in a British cohort [5], 32% in a Greek cohort [14], and 38% in a combined North American/Dutch cohort [3]. However, the yield of family screening in ARVC is highly variable because of its age-related and incomplete penetrance. In a large cohort of 274 first-degree ARVC relatives, symptomatic mutation-carrying siblings of the proband had the highest risk of developing ARVC [6]. In this same cohort, female sex was independently associated with ARVC diagnosis. This female predominance was unexpected and possibly explained by a difference in sex hormones, physical activity, or a different tendency in seeking medical care. In addition, it is noteworthy that while females more often developed ARVC, males were more likely to experience sustained ventricular arrhythmias.

When a genetic (pathogenic or likely pathogenic) variant has been identified in the proband, cascade genetic testing can be offered to first-degree relatives of an ARVC patient. Clinical guidelines recommend a multidisciplinary approach and comprehensive genetic counseling [27]: this avoids unnecessary patient anxiety and decreases the risk of variant misinterpretation [63–65]. Of note, even among individuals known to carry a familial pathogenic variant (e.g., mutation), the clinical heterogeneity of disease complicates prediction of ARVC development. Therefore, a full clinical evaluation is recommended in all at-risk individuals. As outlined in the "HRS Expert Consensus Statement on Evaluation, Risk Stratification and Management of Arrhythmogenic Cardiomyopathy," all relatives should undergo clinical evaluation every 3–5 years including 12-lead ECG, ambulatory ECG, and cardiac imaging [27]. Given the uncertainties regarding sex-related differences in ARVC penetrance, current recommendations do not distinguish between sexes and the aforementioned screening regimens (methodology and intervals) are applicable to both male and female patients.

Risk stratification

The most feared complication of ARVC is sustained ventricular arrhythmia leading to sudden cardiac death. Over the years, many basic science studies have attempted to resolve the final common pathway leading to this outcome (summarized in Ref. [66]), but a cure for ARVC has not yet been found. Until such definite treatment is established, mainstay therapies include exercise restriction and medication (β-blockers or antiarrhythmic agents). The only treatment proven to decrease mortality, however, is an ICD [11,67].

ICD implantation in secondary prevention patients (i.e., cardiac arrest survivors or patients who experienced a sustained ventricular arrhythmia) is widely recommended [11,27]. However, implantation of an ICD for primary prevention purposes is more controversial. A recent study including 110 ARVC patients (43 primary prevention cases) performed a detailed analysis on the impact of sex on prognosis of ARVC and showed that male ARVC patients had a twofold higher risk of VT/VF than female patients [19]. Several other studies confirmed these findings, as summarized in a recent metaanalysis [10]. However, most studies were single-center analyses with a limited number of patients, complicating the potential to draw definite inference about their results. Recently, experts from five major ARVC registries joined efforts to obtain a model for individualized risk prediction in ARVC. As shown in Fig. 32.4, accurate prediction of 5-year risk of sustained ventricular arrhythmias was obtained using seven clinical risk factors: age, sex, recent syncope, nonsustained VT, Holter premature ventricular complex count, T-wave inversions, and RV ejection fraction. In this model, which is available at www.arvcrisk.com, the hazard ratio for male sex was 1.63 (95% confidence interval 1.17–2.29), which translated to a β-coefficient of 0.49 in the model. Hence, while comprehensive sex-based therapies for ARVC management are lacking, distinct management recommendations for male and female patients are on the horizon.

Pregnancy

With average age of diagnosis in the mid-30s, ARVC affects a sizable number of women of childbearing age. As noted in the natural history section, ARVC patients usually present with symptoms related to ventricular arrhythmias rather than those of heart failure and have low annual mortality. Unsurprisingly, many of these women consider pregnancy. This is a multifaceted decision taking into account both pregnancy-related and long-term maternal risks, as well as anticipated obstetric outcomes.

As described earlier, in ARVC patients and genotype positive at-risk family members, vigorous endurance exercise is associated with ventricular arrhythmias and structural progression. Pregnancy is similarly a state of prolonged hemodynamic stress, raising the question of the influence of pregnancy on not only pregnancy outcomes but also on long-term disease trajectory.

Recently, a series of studies have been published addressing these questions. The first, by Hodes et al. [68], reported outcomes of 39 singleton pregnancies in 26 women diagnosed with ARVC before or during pregnancy. Outcomes are shown in Fig. 32.5. Five pregnancies were complicated by single episodes of sustained ventricular arrhythmia, four in the first trimester. All occurred in probands without a history of sustained ventricular arrhythmias

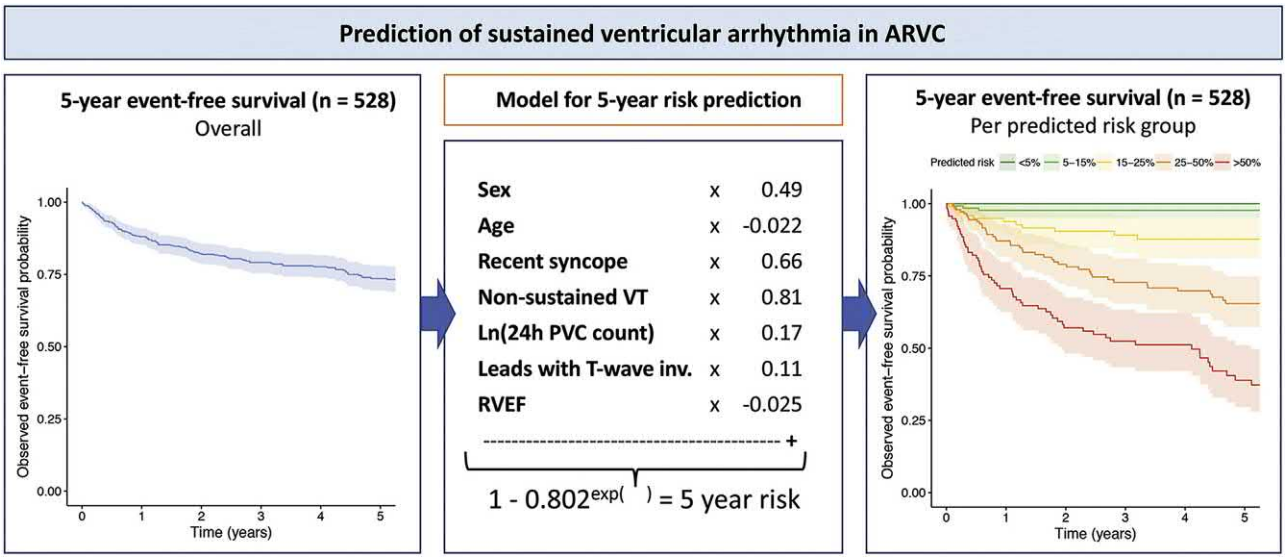

FIGURE 32.4 Individualized risk prediction for sustained ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy (ARVC). Overall risk of ventricular arrhythmia in the whole population (left panel), risk prediction model (middle panel), and resulting arrhythmic risk stratified by risk group (right panel) are shown. *From Cadrin-Tourigny, Bosman, Nozza, Wang, Tadros, Bhonsale et al. A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy, Eur Heart J 2019; 40:1880–1858, by permission of Oxford University Press.*

and two followed β-blocker interruption. Two pregnancies of primagravidae were complicated by new onset heart failure in the second trimester. One of these patients entered pregnancy with biventricular ARVC and a reduced left ventricular ejection fraction. The other had worsening tricuspid regurgitation. All babies were well at last follow-up. Birth weight was significantly lower among mothers who had used β-blocker therapy. The authors also compared long-term (median 8-year) outcomes of these women compared with female ARVC patients of childbearing age who did not have a pregnancy while diagnosed. Results showed no difference in disease course or likelihood of death or transplant in follow-up.

Castrini et al. [69] assessed the relation between number of pregnancies of 43 ARVC patients and 34 genotype-positive relatives on long-term outcomes nearly 20 years after the last pregnancy. Nearly all patients had experienced their pregnancies before their ARVC diagnosis. This study found that the number of pregnancies was not associated with worse right or left ventricular function in follow-up or with an increased risk of long-term ventricular arrhythmias.

Finally, Gandjbakhch et al. [70] reported outcomes of 60 pregnancies in 23 ARVC patients, all but 11 before diagnosis. Two pregnancies were complicated by sustained VT, none by heart failure. Newborns exposed to β-blockers during pregnancy had lower birth weights, but babies were otherwise well. However, at last follow-up, seven of the resulting children had experienced cardiac events including five sudden cardiac deaths.

Taken together, these results suggest that most pregnancies in women with or at-risk ARVC are tolerated well, even among women with a prior history of ventricular arrhythmias or isolated right ventricular structural disease. However, patients with preexisting biventricular disease are likely at considerable risk of developing heart failure. As expected for such an arrhythmic disease, some ARVC pregnancies are complicated by ventricular arrhythmias.

There are no disease-specific guidelines for managing pregnancies in women with ARVC. It is the practice of our programs to optimize preconception arrhythmia management using drugs with low fetal toxicity. ICD implantation, if indicated based on prepregnancy risk factors [10,11,40], should be done preconception. Preconception assessment of biventricular function is helpful as patients with left ventricular dysfunction appear to be at risk for poorer outcomes. Vaginal delivery appears reasonable in many cases. Genetic counseling to discuss the heritable nature of ARVC should also be offered. Finally, the sobering results of Gandjbakhch and colleagues of five sudden deaths in the offspring remind us of the importance of ongoing familial cascade screening for ARVC as recommended in multiple ARVC treatment and management guidelines [27,71].

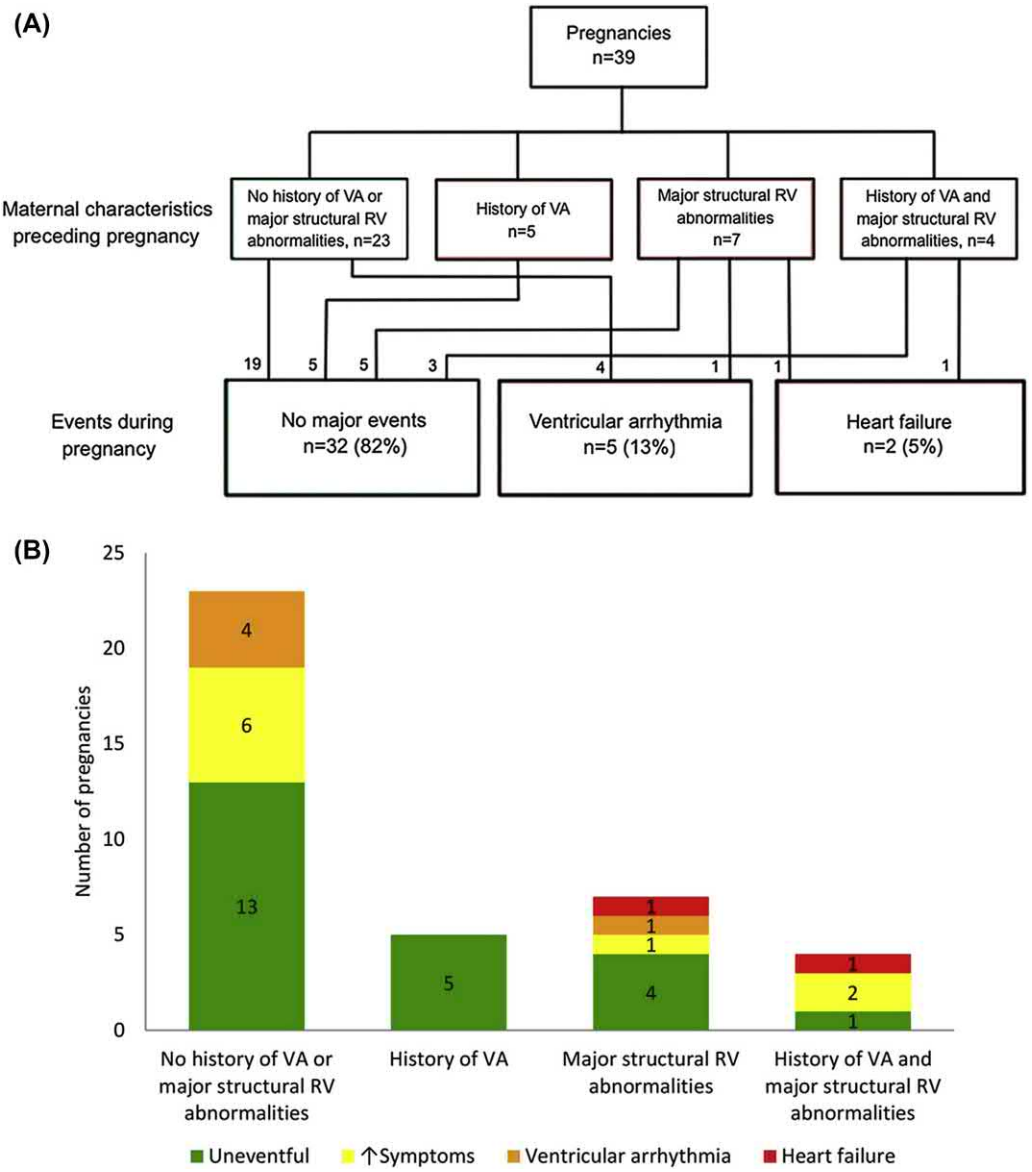

FIGURE 32.5 Outcomes after 39 singleton pregnancies in female arrhythmogenic right ventricular cardiomyopathy (ARVC) patients. (A) Clinical course of ARVC patients shows that most pregnancies were without major cardiac events. (B) Outcomes stratified by medical history at time of pregnancy onset (X-axis). Worsening cardiac symptoms occurred in the absence of cardiac events in nine pregnancies (yellow bars), while five patients experienced ventricular arrhythmias (orange bars) and two patients developed heart failure (red bars). *From Hodes, Tichnell, Te Riele, Murray, Groeneweg, Sawant et al. Pregnancy course and outcomes in women with arrhythmogenic right ventricular cardiomyopathy. Heart February 15, 2016; 102(4):303–312, by permission of BMJ Publishing Group Ltd.*

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Chapter 33

Sex differences in catecholaminergic polymorphic ventricular tachycardia

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Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare, inheritable, arrhythmogenic, and cardiac ion channelopathy. The prevalence is uncertain, but the estimate most commonly referred to is 1:10,000 and is based on the study by Leenhardt and co-workers [1]. Patients often experience syncope or palpations during physical activity or emotional stress, but sudden cardiac death may also be the first symptom [2]. In this chapter, we will review the literature on sex differences in CPVT including clinical presentation, arrhythmic events, disease penetrance, inheritance patterns, and cellular mechanisms.

Genetics and pathophysiology

Mutations in the ryanodine receptor-2 (RyR2) gene are the most common genetic findings in CPVT and are inherited as an autosomal dominant trait. RyR2 mutations are detected in about 60% of clinically diagnosed CPVT patients [3]. The RyR2 is important for calcium-induced calcium release in the cardiomyocytes, and mutations typically cause "leaky" receptors, diastolic calcium overload, and an increased propensity of arrhythmias during catecholaminergic release, e.g., physical or emotional stress [2] (Fig. 33.1). Also, a rare form of CPVT with autosomal recessive inheritance pattern has been described, with mutations in the calsequestrin 2 gene [4]. Calsequestrin 2 is important for calcium storage in the sarcoplasmic reticulum (SR) and for regulation of RyR2 [2].

Sex differences in clinical presentation and arrhythmic risk

Patients with CPVT are characterized by syncope or palpations during physical activity or emotional stress, but sudden cardiac death may also be the first symptom [2]. Clinical examination is usually normal, including resting ECG, echocardiography, and coronary angiography, and the condition is easily overlooked. Family history often reveals relatives with exercise-related sudden cardiac death or recurrent syncope in young individuals [5] and is an important diagnostic clue. An exercise stress test is the

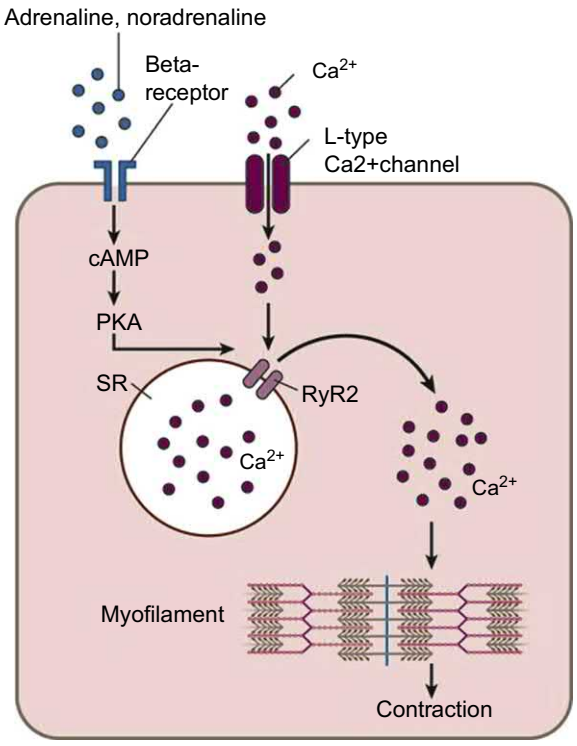

FIGURE 33.1 Cardiomyocyte with β-receptor showing how catecholamines affect the ryanodine receptor-2 and induce calcium leakage from the sarcoplasmic reticulum. *From Leren, IS et al. Tidsskr Nor Legeforen 2010;130:139–142, with permission.*

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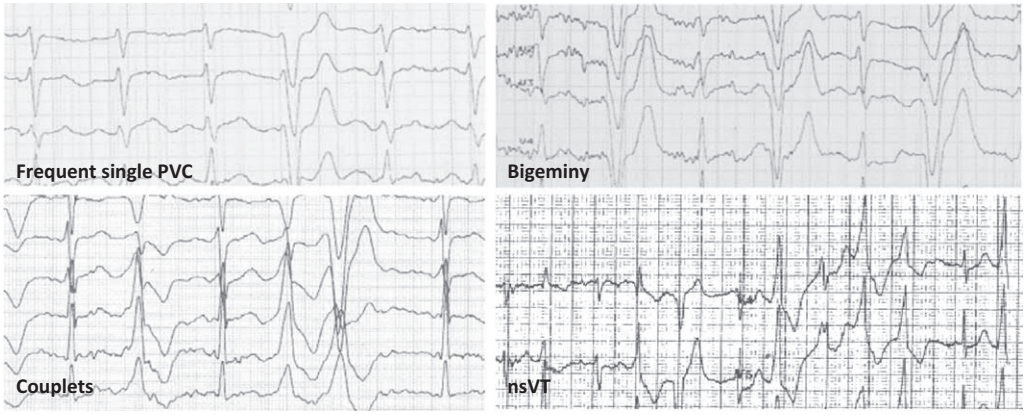

FIGURE 33.2 Typical ECG findings during exercise stress testing in a catecholaminergic polymorphic ventricular tachycardia patient.

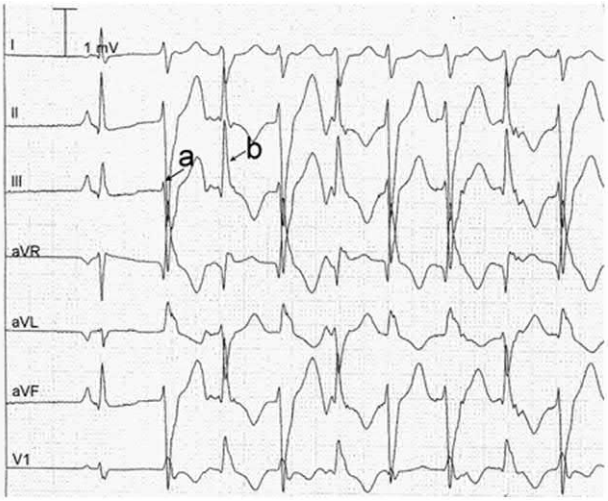

FIGURE 33.3 Bidirectional ventricular tachycardia in a catecholaminergic polymorphic ventricular tachycardia patient. *Arrows* a and b indicate ventricular complexes with change in axis. *From Leren, IS et al. Tidsskr Nor Legeforen 2010;130:139–142 with permission.*

most sensitive clinical tool, revealing excessive premature ventricular beats during exercise [6–8]. Premature ventricular beats typically appear at a heart rate of 110–130 [7] and the severity of arrhythmias increases with increased workload [9], (Fig. 33.2) sometimes resulting in a bidirectional ventricular tachycardia (Fig. 33.3) that might degenerate to ventricular fibrillation, causing syncope or even sudden cardiac death.

Studies regarding sex differences in clinical presentation are rare, include a limited number of patients, and the results differ. In 2002, Priori and co-workers [5] presented data on 23 patients with RyR2 mutation-positive CPVT and found that male patients more frequently reported syncopal episodes (11/13 male vs. 2/10 female). Based on this, the authors estimated a relative risk of syncope of 4.2 in male compared with female patients, and they proposed early genotyping in children of affected patients, as the combination of male sex and RyR2 mutations constitutes individuals at high arrhythmic risk. This study is often referred to as showing that male patients are more prone to malignant arrhythmias. However, in nongenotyped CPVT, the same study showed that female sex was predominant (18/20), also when analyzing only symptomatic subjects. Importantly, the study did not state that CPVT is neither more malignant nor more penetrant in male patients in the patient group as a whole. Bauce and co-workers [10] reported on 43 RyR2-positive CPVT subjects, 25 female and 18 male. Among 28 patients presenting with effort-induced arrhythmias, 15 were female and 13 male, and among asymptomatic individuals, 10 were female and 5 were male. In summary, no sex differences in clinical presentation or arrhythmic status could be identified (Fig. 33.4). Therefore, this study could not replicate the findings from Priori et al. [5]. Analyses of the pedigrees of included families showed that among 19 sudden deaths, 12 were male and 7 female. Further statistics or total number of male and female relatives was not presented, and the interpretation regarding sex differences was limited. Laitinen and co-workers [11] also reported similar number of affected male and female patients (12 vs. 14 patients) in their study, but did not comment further on possible sex effects.

In summary, studies including sex differences in clinical presentation in CPVT patients, including RYR2 positive cohorts, were small and results diverging. There are no certain conclusions on sex differences in arrhythmic risk in CPVT, and across studies there is no clear evidence that male sex is a risk factor for arrhythmic events.

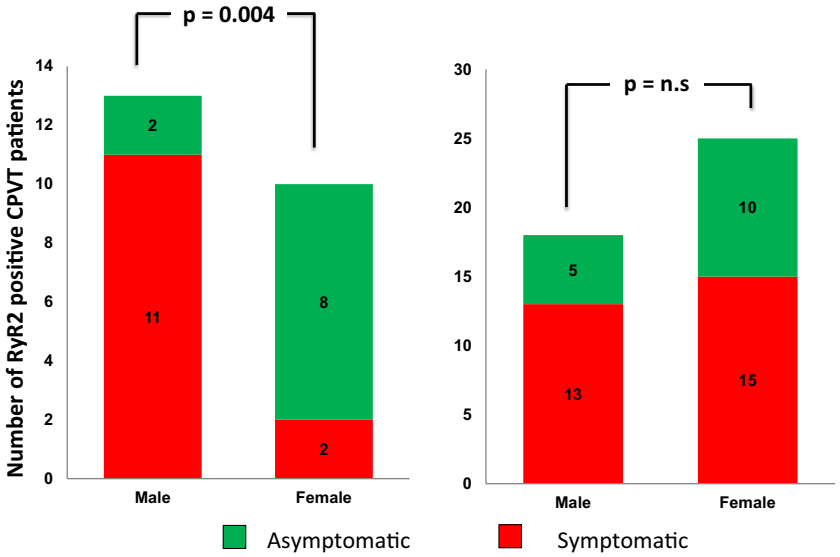

FIGURE 33.4 RyR2-positive catecholaminergic polymorphic ventricular tachycardia (CPVT) patients from Priori et al. (left) and Bauce et al. (right). Priori found more symptomatic male patients compared with female, but Bauce did not replicate these findings.

Sex differences in disease penetrance

Inheritance in RyR2 mutation-positive CPVT is autosomal-dominant and as such does not discriminate between the sexes. However, in, e.g., hypertrophic cardiomyopathy, the penetrance is higher in men despite the autosomal dominant inheritance pattern, exemplifying that autosomal dominant inheritance does not necessarily imply similar disease burden between the sexes. Variable penetrance has been reported in several small studies on CPVT patients and between different specific mutations [10,12]. However, Bauce and co-workers concluded in their study that the different penetrance in arrhythmic signs and symptoms depended neither on age nor sex [10].

Interestingly, sex differences in inheritance mode of RyR2 mutations have been suggested [13]. Ohno and co-workers reported that in 26 families, more than 50% of patients had de novo RYR2 mutations, and in the majority of the remaining patients, mutations were inherited from mothers (7/26 maternal inheritance vs. 2/26 paternal inheritance). The authors speculated that this could be explained by worse prognosis in male versus female patients and that male CPVT patients might die before reaching reproductive age. However, numbers were very limited and not supported by others: In the cohort of Priori and co-workers [5], 2/14 patients were found to have maternal inheritance and 1/14 paternal inheritance. Van der Werf and co-workers [12] also reported similar proportions of maternal and paternal inheritance (6/17 vs. 5/17). In summary, results suggest a substantial proportion of de novo mutations with no clear sex differences in inheritance mode or penetrance of disease.

No sex differences have been observed in the even more rare form of CPVT caused by mutations in the calsequestrin gene, which is inherited in an autosomal recessive pattern [4].

Treatment of ventricular arrhythmias in CPVT

β-Blockers are mainstay of treatment in CPVT patients and a Class I C recommendation in both male and female clinically diagnosed patients [14]. Catecholaminergic stimulation of the β-receptor aggravates pathological diastolic calcium release from the mutated, unstable RyR2 channel, causing malignant ventricular arrhythmias [2]. β-Blockers are suggested to provide arrhythmic protection by reducing the influence of catecholamines by blocking the β-receptor−induced intracellular signaling which leads to destabilization of RyR2 [15]. Nadolol seems to be the most potent β-blocker in suppressing ventricular premature beats during exercise [16]. When arrhythmic control is incomplete on β-blockers alone, the guidelines suggest adding flecainide (Class IIa C) [14]. An implantable cardioverter defibrillator is recommended in patients who experience cardiac arrest, recurrent syncope, or ventricular tachycardia despite optimal medical therapy (Class I C), and furthermore, left cardiac sympathetic denervation may be considered (Class IIb C).

Recommendations for treatment are similar in men and women, although some authors suggest being extra attentive in young males, as some studies have indicated that they have a higher risk of cardiac events [5]. Importantly this only refers to RyR2-positive CPVT subjects and is not shown in gene-elusive CPVT patients. Catecholaminergic stimuli are mandatory for triggering arrhythmias in CPVT patients, and one might speculate that behavior of young males is more likely to include intense physical activity, thereby partly explaining the difference observed in some studies.

Experimental studies on sex differences in CPVT

Animal studies on sex differences in CPVT-specific models are lacking. However, the studies on the impact of sex on cardiac contractile function elucidate potential sex differences in RyR2 expression and function, elaborated in this paragraph [17].

It has been discussed whether the abundance of RyR2 channels differs between the sexes. Two studies on RyR2 expression levels in rat ventricles showed higher RyR2 levels in female compared with male cardiomyocytes [18,19].

The sex-specific response of myocytes to β-adrenergic receptor activation has been studied. Animal studies showed that myocytes from male animals respond to the nonselective β-adrenergic receptor agonist, isoproterenol with a larger increase in contractions, Ca^{2+} transient amplitudes, and Ca^{2+} current compared with females [20,21]. Isoproterenol also caused a larger increase in diastolic Ca^{2+} and SR Ca^{2+} content in cardiomyocytes from males [21]. Furthermore, diastolic Ca^{2+} levels were significantly lower in cardiomyocytes from female rats when compared with male rats [22]. These findings gave rise to speculations that there could be a greater propensity for arrhythmias in males with CPVT, as diastolic calcium leaks during adrenergic stimulation is an important part of arrhythmogenesis. Further studies are required to fully understand the mechanisms that underlie sex differences in response to β-adrenergic receptor activation [17].

Other animal studies have indicated that peak cardiac contractions are smaller and slower in intact hearts and cardiac muscle preparations from females when compared with males. The magnitude of cardiac contractions and underlying Ca^{2+} transients depends upon SR Ca^{2+} content [17]. One theory proposed a higher SR calcium content in males compared with females with a higher amount of calcium released from a leaky RyR2 in male, thus explaining an eventual increased propensity for arrhythmias in male CPVT. The hypothesis of different SR calcium levels has been investigated in several animal models, but studies in mice and rats showed no sex differences, whereas in guinea pigs, SR calcium content was higher in female animals [17]. Altogether, there is no evidence for sex differences in cellular mechanisms affecting patients with CPVT.

Conclusions

CPVT is a relatively rare disease and studies include a limited number of patients. At present, there is no clear evidence of sex differences in clinical presentation, arrhythmic risk, disease penetrance, or mode of inheritance in CPVT. While some studies report higher risk of ventricular arrhythmias in male patients and a higher maternal inheritance, other studies have not been able to support these findings. Treatment strategies and risk stratification do not currently include sex-specific advice. Animal studies have elucidated mechanistic aspects of excitation–contraction coupling, but no clear sex differences in RyR2 regulation or calcium load in the SR have been established. Whether sex differences are absent in CPVT, or not evident because of lack of power in limited studies, is uncertain and remains to be further studied in larger multicenter studies.

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Chapter 34

Cardiac electrophysiology in sex chromosome aneuploidies

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Introduction

Males and females are fundamentally different in their normal biology and pathophysiology. These well-established differences have almost exclusively been attributed to the effects of circulating gonadal sex hormones [1–3]. The presence of two X chromosomes in females (XX) and one X chromosome and one Y chromosome in males (XY) represents our most fundamental genetic polymorphism. Recent work has begun to highlight the potential contribution of sex chromosome complement to male–female beyond the reproductive tract [4,5].

Sex bias in susceptibility and severity has been observed in many human diseases, including those that affect the conduction system of the heart. Females have a higher risk of developing atrioventricular nodal reentry tachycardia [6]. Males have a higher incidence of sudden cardiac death [7]. Most of the work studying the mechanisms that lead to such differences has focused on the role of sex hormones, while largely overlooking the potential influence of sex chromosome complement [8].

Although euploid 46, XX (female) and 46, XY (male) are the most common human karyotypes, variation in sex chromosome complements is a relatively common phenomenon in the human population affecting 1 in 1834 individuals [9]. These individuals present with loss or gain of sex chromosomes and manifest clinically with a spectrum of cardiovascular and noncardiovascular phenotypes.

This chapter aims to review the evolution of human sex chromosomes and the electrophysiological manifestations of having too many or too few. Not only does the work reviewed here allow better understanding and clinical management of these patients but it may also be harnessed to help elucidate the contributions of sex chromosome complement and sex hormones in electrophysiological differences between euploid males and females.

Evolution of human sex chromosomes

Sexual reproduction is a near-ubiquitous feature of eukaryotic organisms allowing the creation of a new organism by combining the genetic information of two individuals. While some animals are hermaphrodites, most of the kingdom has evolutionary segregated male and female reproductive organs into individuals of two district sexes [10]. Sex determination can be achieved environmentally through an extrinsic stimulus such as temperature or nutrient availability. This form of sex determination is common among reptiles and crustaceans. In most animals, sex determination is encoded by genomic elements [11].

In mammals, including humans, sex is determined by a pair of heteromorphic sex chromosomes, the X and Y. The modern-day human X and Y chromosomes are a product of at least 168 million years of evolution (Fig. 34.1) [12,13]. They evolved from a pair of homologous autosomes that still exist in birds today. The first step on the journey of mammalian sex chromosome evolution involved a series of mutations that resulted in the creation of SRY, a testis-determining gene on the proto-Y chromosome [14,15]. Subsequently, the appearance of sexually antagonistic alleles near SRY and a series of chromosome inversion events provided the selective pressure to suppress recombination between the proto-X and proto-Y chromosome. In the absence of crossing over, the male-specific region of the Y chromosome (MSY) was subjected to genetic decay. The extant human Y chromosome has lost most of its ancestral gene content, with only 17 ancestral genes surviving. In contrast, the X chromosome has prospered, retaining most of its ancestral gene content [4].

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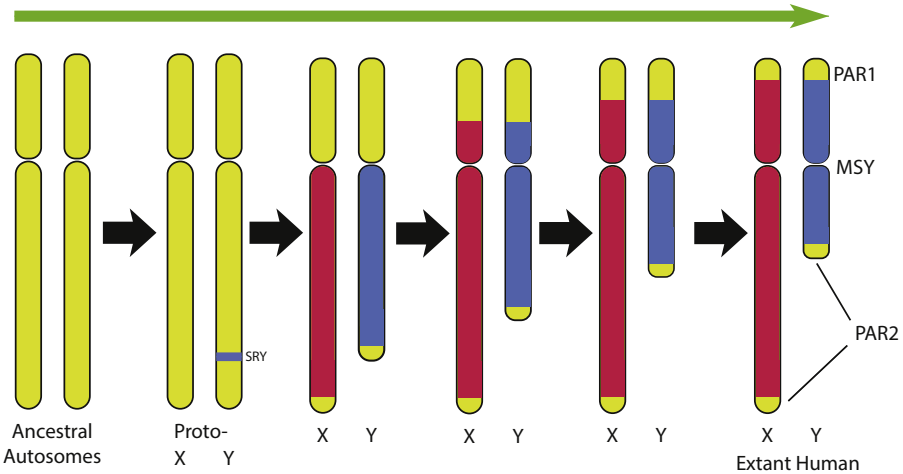

FIGURE 34.1 Evolution of human sex chromosomes. Mammalian sex chromosomes originated from a pair of autosomes. ~168 million years ago (Mya) *SRY* was acquired on an autosome triggering Y-chromosome differentiation. Recombination was suppressed by emergence of sexually antagonist alleles and a series of inversion events. Exclusion from recombination led to rapid degradation of the male-specific region on the Y (MSY), leaving only small pseudoautosomal regions (PAR1 and PAR2) that still undergo recombination.

Sex chromosome effects on sexual dimorphism

X-chromosomal effects: mosaicism, skewing, imprinting, and escape

The X chromosome is one of the largest and most gene-rich human chromosomes. Females carry two X chromosomes, and males carry a single copy of the X chromosome and a diminutive Y chromosome. As such, the difference in X-linked gene dosage has resulted in the evolution of compensatory mechanisms to balance X-linked gene expression between the sexes and to balance X-chromosome expression with autosomes [16]. Transcription of X-linked genes is upregulated twofold to maintain an equal X:A expression ratio in both sexes [17] and in females one of the X chromosomes is transcriptionally silenced through X-chromosome inactivation (XCI) [18]. The process of XCI in females offers several potential mechanisms that can contribute to phenotypic sexual dimorphism.

XCI is mediated by the long noncoding RNA XIST that coats the X chromosome in cis, ultimately resulting in transcriptional silencing [19]. XCI is random in periimplantation human embryos resulting in silencing of either the maternally derived (Xm) or paternally derived (Xp) X chromosome [20]. Females are therefore mosaics of cells expressing either Xm or Xp (Fig. 34.2A). In contrast, males only inherit their X chromosome from their mothers, resulting in exclusive expression from Xm. For this reason, males have fully penetrant phenotypes in X-linked recessive disorders, whereas females can present with phenotypic variation.

Theoretically, random XCI should result in an equal distribution of cells in a female, which inactivate Xm or Xp. Skewing of XCI is a common phenomenon in the general human population and is mostly tissue specific [21–23]. As a result of this skewing, the proportion of cells expressing a given X-linked allele can vary in females resulting in a potential molecular mechanism for sex difference compared to males that only express Xm (Fig. 34.2B). Skewing has been implicated in several autoimmune conditions that are more common in females, including scleroderma [24], rheumatoid arthritis [25], and autoimmune thyroiditis [26].

Similarly, genomic imprinting results in monoallelic expression of genes in a parent-of-origin–specific manner [27]. Females inherit X chromosomes biparentally, whereas males only inherit their X chromosome from their mothers. An imprinted gene on Xp would therefore never be expressed in male cell and would be expressed in half of the female cells. In contrast, an imprinted gene on Xm would be expressed in all cells of the male and half of the female cells (Fig. 34.2C). Genomic imprinting is a common phenomenon on autosomes [28], but an imprinted X-chromosome locus in humans has yet to be discovered. If imprinting does take place on the human X chromosome, it would represent a fundamental mechanism for sexual dimorphism that could result in phenotypic sex differences.

Finally, around a third of X-linked human genes escape XCI (Fig. 34.2D) and show variable expression with substantial intertissue variability [21,29]. Some of these escapees are located within the pseudoautosomal region (PAR), an area of homology between the X and Y chromosome, where copy number is equal. Escape genes also reside outside the PAR with many displaying female-biased expression. The difference in dosage between X-linked genes between the sexes could account for male–female phenotypic variation. A recently discovered example of this includes the X-linked escapee toll-like receptor 7 (TLR7). Increased TLR7 dosage in female myeloid lineage cells due to XCI escape contributes to the development of systemic lupus erythematosus, a disease with a strong female sex bias [30].

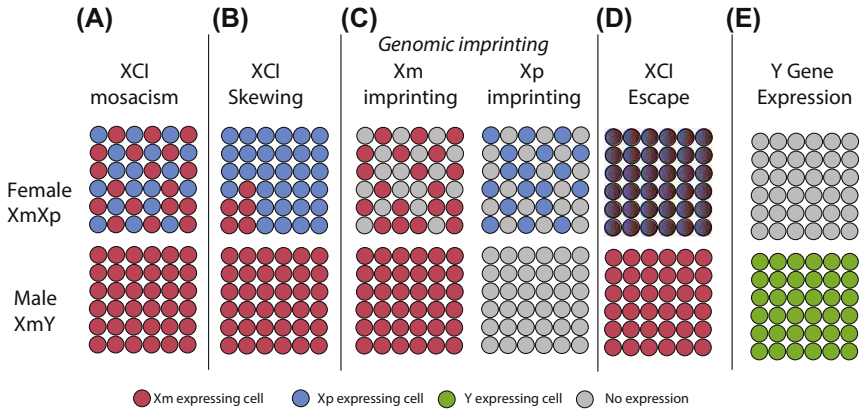

FIGURE 34.2 Mechanisms to explain genetic sex differences. Each square of *circles* represents a selection of cells in females (top row) and males (bottom row). Color of *circles* corresponds to legend. For simplicity, assume that each gene is ubiquitously expressed (Xm: maternally derived X chromosome; Xp: paternally derived X chromosome). (A) Due to XCI, there is an approximately equal distribution of cells that express Xp and Xm alleles in females. All male cells express Xm alleles. (B) Skewing of XCI can result in an altered proportion of female cells expressing a particular allele. In the case depicted, there is a skewing in favor of the Xp allele. (C) Genomic imprinting of Xm results in expression from half of cells in females and all cells in males. Imprinted expression of an Xp allele results in expression from half of cells in females and no cells in males. (D) XCI escape results in biallelic expression of Xm and Xp in female cells. In males, only Xm is expressed. (E) Y-linked genes are only expressed in male cells.

Y-chromosomal effects: functional divergence of X−Y gene pairs

The Y chromosome has been decimated throughout evolution, losing most of its ancestral gene content [12,13]. It has instead become a specialized hub for genes required for spermatogenesis and sex determination. Past investigation of Y-chromosome biology has been confined to the cells of the reproductive tract with the view that it makes little impact outside the male gonad.

Recent insights in comparative sequence analysis of the Y chromosome have shown that it is home to a small number of ubiquitously expressed ancestral genes that survived sex chromosome evolution (Fig. 34.2E). Intriguingly, these survivors encode proteins that are involved in the regulation of basic biochemical processes, including regulators of splicing, transcription, translation, and protein degradation [12,13]. These regulators are dosage-sensitive and have X-linked homologs that escape XCI. These X−Y gene pairs are of great interest as a subtle functional divergence between X−Y protein isoforms could have significant consequences in the phenotypic differences between males and females.

Aneuploidy

Aneuploidy encompasses the loss (monosomy) and gain (trisomy/polysomy) of chromosomes. Autosomal monosomies are not compatible with life. Three autosomal trisomies survive, albeit with severe phenotypes, including varying degrees of intellectual disability and developmental abnormalities. Trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome) fetuses survive to term but are only viable for weeks to months. Trisomy 21 (Down syndrome) is a better-tolerated trisomy but is associated with high rates of morbidity and mortality, resulting in a life span of approximately 50 years [31].

In contrast, sex chromosome aneuploidies are commonplace and can be associated with a normal life expectancy. The only viable monosomy is that of the X chromosome, and sex chromosome trisomies are common in the human population. The phenotypes exhibited in these sex chromosome aneuploidies are wide-ranging with many patients escaping diagnosis due to their asymptomatic nature [32].

Sex chromosome aneuploidies are categorized into those that affect biological females and those that affect biological males. There are situations whereby sex is reversed, and the sex chromosome complement is not commensurate with reproductive anatomy, but these instances are relatively uncommon and go beyond the aims of this chapter.

Sex chromosome aneuploidies in biological females

Sex chromosome aneuploidies in biological females present with loss or gain of X chromosomes and the absence of a functional Y chromosome.

Turner Syndrome (45, XO)

The most commonly diagnosed sex chromosome aneuploidy in biological females is X-chromosome monosomy, Turner syndrome (45, XO). Turner syndrome affects 1 in 2500 females. Complete 45, XO monosomy occurs in approximately half of patients, but Turner syndrome can exist in many karyotypic forms including mosaicism (45, XO/46, XX; 45, X/47, XXX) and structural X chromosome

abnormalities, including X isochromosome, ring chromosome, or deletions [33].

Turner syndrome females share a core phenotype of neck webbing, congenital cardiovascular/renal abnormalities, short stature, and gonadal dysgenesis. Phenotypes between individuals can be wide-ranging, resulting in diagnostic delay, which is unfortunate, as Turner syndrome is associated with higher levels of morbidity and mortality than the general population. The risk of premature death is increased threefold in Turner syndrome females with life expectancy reduced by at least a decade [34].

Cardiovascular disease is the leading cause of morbidity and mortality in Turner syndrome. Girls and women experience both congenital heart disease and acquired cardiovascular disorders [34]. Congenital heart abnormalities occur in up to half of Turner syndrome females. The most common abnormalities include a bicuspid aortic valve, coarctation of the aorta, and thoracic aortic aneurysm [33]. Transthoracic echocardiography has been the mainstay imaging technique to identify and monitor congenital abnormalities in Turner syndrome patients. Computerized tomography and cardiac magnetic resonance imaging are now increasingly being used as more sensitive imaging techniques to identify subtle abnormalities [35]. Congenital abnormalities of the heart are associated with conduction defects and extensive myopathic changes in animal models and patients [36], leading to speculation that developmental abnormalities in Turner syndrome patients can affect their electrophysiology.

Differences in the electrocardiogram (ECG) between Turner syndrome individuals and the general population are well documented. Sinus tachycardia is a lifelong phenomenon [37,38]. Atrioventricular node conduction is accelerated associated with a risk of atrial tachycardia [38]. Several ECG abnormalities are present in Turner syndrome females. These are numerous and include right axis deviation, T-wave abnormalities, short PR interval, and accelerated atrioventricular AV conduction [33]. In a pediatric setting, right axis deviation is associated with the presence of partial anomalous pulmonary venous connection [39].

In Turner syndrome females, the myocardial action potential is prolonged with delayed repolarization. A prolongation in QT interval is a consistent finding among patients of all age groups [39–41] (Fig. 34.3). In the general population, QTc prolongation is associated with increased risk of ventricular arrhythmias and sudden cardiac death. A single case report has highlighted a sudden death after a dose of amiodarone resulted in QTc prolongation and subsequent cardiac arrest. There is limited evidence for fatal arrhythmias in Turner syndrome patients, and the QTc prolongation observed may not put them at increased risk, as QTc resolves during exercise stress testing [39]. Nevertheless, clinical guidelines recommend that exercise testing and Holter monitoring should be considered for risk estimation in patients with prolonged

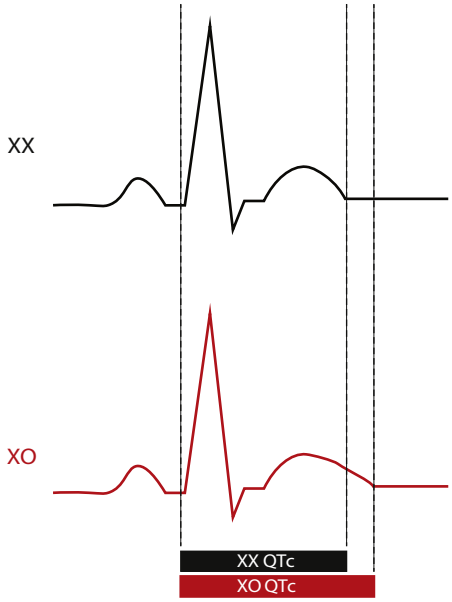

FIGURE 34.3 Women with Turner Syndrome have a longer QTc compared with female controls.

QTc [42]. Interestingly, a recent study has demonstrated a correlation between Turner syndrome and gene variants associated with long QT syndrome [43]. It remains to be investigated whether this finding is associated with the higher incidence in cardiovascular mortality and morbidity in Turner syndrome patients. To support clinical data, in vitro work in Turner syndrome induced pluripotent stem cell (iPSC) models has demonstrated that Turner syndrome iPSC-derived cardiomyocytes have prolonged action potential compared to euploid control cells [44].

Complete monosomy 45, XO is associated with longer QTc compared to Turner syndrome mosaics. Complete 45, XO is also associated with increased severity in a number of Turner syndrome phenotypes including congenital heart disease, suggesting that mosaicism to some degree ameliorates the phenotype [45].

Triple X syndrome (47, XXX) and X chromosome polysomies

Triple X syndrome is the most common sex chromosome aneuploidy in biological females, affecting 1 in 2000. The condition is associated with a tall phenotype, with adolescents reaching the top percentiles of height. Unlike Turner syndrome, most triple X syndrome patients enter puberty normally and are fertile. Triple X females are therefore commonly asymptomatic, and diagnosis is often only due to an incidental finding [46]. Cardiovascular congenital defects are rare in triple X syndrome and do not exceed the prevalence in the general population [47]. The main clinical phenotypes that have been reported in triple X females

include auditory processing disorders and disorders of language development [46]. Electrophysiological disturbances of the neurological system have been reported in triple X females with epilepsy and EEG anomalies [48]. Currently, there are no cardiovascular electrophysiology studies in triple X syndrome patients.

48 XXXX and 49, XXXXX are rare sex chromosome aneuploidies accounting for only a small number of case reports in the literature. These patients are born with craniofacial and skeletal abnormalities of varying degree [49–52]. Unlike triple X syndrome, congenital heart disease is seen [51], but the effect of X-chromosome polysomy on cardiac conduction and electrophysiology still requires investigation.

Sex chromosome aneuploidies in biological males

Sex chromosome aneuploidies in males constitute any variation from euploid 45, XY while retaining at least one functional Y chromosome.

Klinefelter Syndrome (47, XXY)

Klinefelter syndrome was first described in 1942 as a case series of male patients presenting with small testis and gynecomastia [53]. It is the most commonly diagnosed sex chromosome aneuploidy in biological males with an incidence of 1 in 600 male newborns [54].

Klinefelter syndrome neonates rarely have dysmorphic features and children generally do not present with any pathological features. As the individual enters adolescence, signs of the condition begin to present themselves. Klinefelter syndrome males have tall stature and female distribution of adipose tissue. Klinefelter syndrome men have gynecomastia and decreased facial and pubic hair. Klinefelter syndrome is the most common male genetic cause of infertility and hypogonadism due to abnormal development of the testis [55]. Although there is some variation in the degree of hypogonadism, most Klinefelter syndrome males have low levels of testosterone [56].

The condition is associated with learning disabilities and reduced IQ as well as an increased risk of development of psychiatric conditions including autistic spectrum disorder [57]. Several studies have shown that morbidity and mortality are increased in Klinefelter syndrome [58,59], and similarly to Turner syndrome, mortality is primarily associated with cardiovascular disease. Recent work has demonstrated an increased risk of congenital heart disease in Klinefelter syndrome patients compared to the general population [58] but to a lesser extent than seen in Turner syndrome females. Examples of congenital heart disease that have been reported in the literature include transposition of the great arteries [60,61] and partial atrioventricular canal defects [62].

Some studies have assessed left ventricular systolic and diastolic function in Klinefelter syndrome hearts. An echocardiographic study of 22 patients identified mitral valve prolapse in 55% [63]. A more recent study could not replicate this finding [64], with no evidence of mitral valve prolapse or difference in left ventricular structure or systolic function when compared to the general population. A further investigation was able to demonstrate only a subclinical alteration in systolic function when strain analysis was employed [65], but a 20% prevalence of diastolic dysfunction.

Investigation of resting ECGs of patients with Klinefelter syndrome has shown shorter QT intervals when compared with controls. [66] QTc was the shortest among testosterone-treated patients. The EXAKT (Epigenetics, X-chromosomal Features and Clinical Applications in Klinefelter Syndrome Trial) corroborated that Klinefelter syndrome men have shorter QTc [67]. This prospective cross-sectional study of a large cohort of Klinefelter syndrome patients and their parents assessed cardiovascular, inflammatory, and metabolic features in patients compared to age-matched female and male controls. The authors demonstrated that QTc was significantly shorter in Klinefelter syndrome patients compared to male euploid controls. Interestingly, this effect was more pronounced in males with a paternal origin of the supernumerary X chromosome, indicating a possible imprinted effect (Fig. 34.4). Unlike the other study, serum testosterone levels were not associated with QTc shortening.

The extent to which cardiovascular and noncardiovascular phenotypes are a consequence of hypogonadism or a direct effect of the supernumerary X chromosome is an open question. Distinguishing the relative impact of hormonal and genetic components is a difficult task. Evidence to support a genetic basis are that features of Klinefelter syndrome present before the onset of hypogonadism. Klinefelter syndrome habitus and disproportionately long legs are present from infancy [68]. Attention and verbal deficits are observed in early childhood and differences in brain volume are seen between prepubertal Klinefelter syndrome children and controls [69]. Testosterone replacement therapy has been shown not to make a significant impact on cardiopulmonary performance, chronotropic incompetence in Klinefelter syndrome [64] compared to the improvement seen in euploid 46, XY males with hypogonadism [70].

Double Y syndrome (47, XYY) and other sex chromosome complements in biological males

47, XYY males have a supernumerary Y chromosome of paternal origin [71] affecting 1 in 1000 males [72]. Double Y males have tall stature, but unlike Klinefelter syndrome males, most are fertile [73]. For this reason, like triple X females, they often go undiagnosed.

Double Y Syndrome patients have increased rates of motor and language difficulties, attention-deficit hyperactivity disorder, and autism spectrum disorder diagnoses

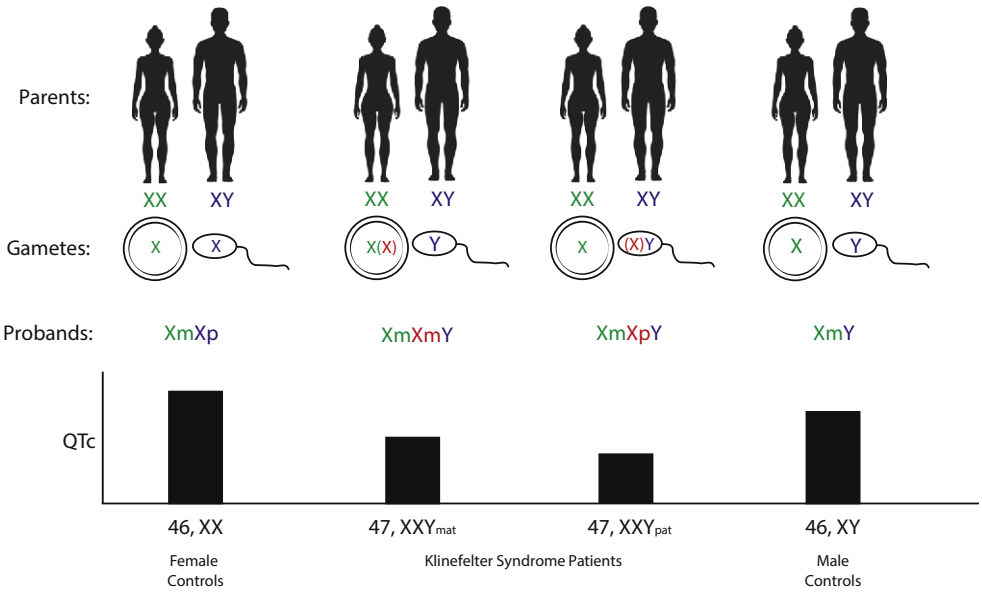

FIGURE 34.4 Errors during gametogenesis can lead to maternal or paternal inheritance of the supernumerary X chromosome in Klinefelter Syndrome (supernumerary X chromosome depicted in red). Simplified overview of EXAKT [67] where QTc is overall lower in Klinefelter Syndrome patients versus male and female controls and an even more pronounced phenotype is seen in Klinefelter Syndrome patients with paternal origin of the supernumerary X chromosome.

[74]. Cardiovascular disease is uncommon in XYY males, and their electrophysiology is not well characterized.

Similar to females, males can have rarer sex chromosome complements, including 48 XXXY, 48 XXYY, 49 XXXXY, and 49 XYYYY [75]. Congenital heart disease is common among these Klinefelter variant sex chromosome complements, but electrophysiological disturbances have not been investigated.

Summary and relevance to euploid sex differences

Sex chromosome aneuploidies are common in the general population, and the loss or gain of sex chromosomes is a relatively well-tolerated phenomenon compared to autosomal aneuploidy.

The best-studied groups of patients with sex chromosome aneuploidies are Turner syndrome females. Congenital heart disease is common in these patients prompting investigation of acquired disturbances of the cardiac conduction system. While Turner syndrome patients have several electrophysiological abnormalities, the feature that has attracted the most attention is that they have extended action potentials with QTc prolongation when compared to euploid female controls. It is unclear at this time whether prolonged QTc observed in Turner syndrome patients is associated with an increased risk of ventricular arrhythmia, as it is in the general population. Klinefelter syndrome males are the next well-investigated group with several studies conducted

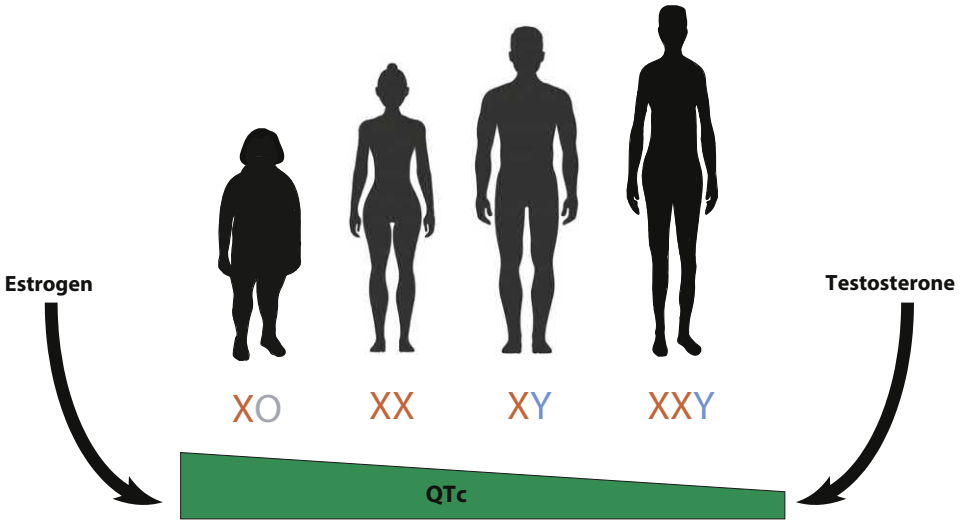

FIGURE 34.5 Complex interplay between sex chromosome complement and sex hormones in sex differences in QTc.

investigating ECG patterns. Interestingly, in contrast to Turner syndrome females, Klinefelter syndrome males have significantly shorter QTc than sex-matched euploid controls.

The finding that individuals with a supernumerary X chromosome have shortened QTc and monosomy X prolongs QTc is intriguing and suggests that an individual's sex chromosome complement has a direct impact on ventricular repolarization. The role of sex hormones on the QTc interval is established. Premenopausal females have significantly longer QTc than age-matched males [76]. Studies have indicated that estrogen has a QTc lengthening effect [77] and testosterone has a shortening effect [78]. The finding that QTc is also augmented in hypogonadal sex chromosome aneuploidy patients requires further investigation.

Sex chromosome aneuploidy patients represent an intriguing model to investigate the complex interplay between sex chromosome complement and gonadal sex hormone status in sex differences such as QTc (Fig. 34.5) that could have direct relevance to male–female differences observed in euploid individuals. To truly understand the mechanistic basis for sex differences, it will be necessary to deconstruct sex into its two component parts: gonadal sex hormone status and sex chromosome complement. This is a challenging undertaking and will require a population-level analysis of individuals with a variety of different sex chromosome complements and hormone statuses. Additionally, it will be necessary to look to experimental models. The four core genotype mouse model whereby gonadal sex and sex chromosome complement are uncoupled has been a popular tool for such experiments [79]. Unfortunately, with more recent knowledge, the mouse may not be a good model to identify clinically relevant genetic mechanisms of sex differences as the mouse and human sex chromosomes are evolutionary and functionally divergent with different cohorts of X–Y gene pairs and X-linked escapees. Therefore, nonhuman primates or recently derived human isogenic pluripotent stem with different sex chromosome complements may offer a more clinically relevant alternative [80]. Only when combining data from human population genetics with these emerging experimental paradigms will it be possible to dissect the complex interplay of the genetic and hormonal basis for sex differences in cardiac electrophysiology and beyond.

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Chapter 35

Takotsubo syndrome

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Clinical features and pathophysiologic aspects of takotsubo syndrome

Takotsubo syndrome (TTS), first described in Japan in 1990 [1], has increasingly been recognized worldwide over the past years. This cardiac syndrome mimics acute myocardial infarction and is characterized by transient left ventricular (LV) regional dysfunction not corresponding to a single coronary artery territory, ischemic electrocardiographic (ECG) changes, and elevation of cardiac markers in the absence of culprit epicardial coronary artery disease. Frequently, this reversible form of acute heart failure is precipitated by a stressful event, consisting of either an emotional or physical trigger [2]. Preceding physical stress (most commonly acute noncardiac illness or surgical/diagnostic procedures) is significantly more frequent in male patients with TTS, whereas emotional stress or no identifiable trigger is more prevalent in women [3−7]. The rate of psychiatric disorders appears to be high in patients with TTS (43%) [6].

According to the distribution of the regional wall motion abnormality, different anatomical variants of TTS have been recognized (Fig. 35.1). The most common type is the classical "apical" pattern with akinesia or dyskinesia of the LV apical and midventricular segments and hypercontractility of the basal segments, accounting for 70%−80% of cases. The midventricular type (about 15% of cases) is characterized by hypo- or akinesia of the midventricular segments, mild hypokinesis, or normal contraction of the apical segments and hypercontractility of the base. The basal or inverted (reverse) TTS variant (2%−5% of patients) shows basal hypokinesia or akinesia and apical hypercontractility, while the focal type (1.5%) is confined to a single LV segment, mostly the anterior or lateral wall [2]. Right ventricular involvement in TTS has been diagnosed in 24%−31% of patients [2,8].

In all studies reported so far, the great majority (80%−90%) of individuals with TTS are elderly postmenopausal women with a mean age of 65−70 years [2,3,5,6,9,10]. In most case series from Western countries, less than 12% of the patients are men. The number of men, however, seems to be higher in studies from Asia ranging from 13% to 35% [7,9,11]. Although in both females and males with TTS the average age is around 65 years, approximately 10% of the patients are below 50 years of age [6,9,12], and even young individuals as well as children of both sexes may be affected [13]. Approximately 1%−3% of all patients with a suspected acute coronary syndrome (ACS) undergoing coronary angiography are diagnosed with TTS [10,14−16]. There is a sex-specific prevalence that is higher in women, ranging from 6% to 9.8%, whereas the prevalence of TTS among male patients with an ACS is below 0.5% [10,16]. It is estimated that there are approximately 50.000−100.000 TTS cases per annum in the United States, with similar estimated numbers in Europe [2,17].

TTS has generally been regarded as a relatively benign disease with rapid recovery of LV dysfunction. However, growing evidence suggests that it is a more serious cardiac disorder with a variety of complications such as acute heart failure, cardiogenic shock, malignant arrhythmias, LV outflow tract obstruction, mitral regurgitation, right ventricular involvement with pleural effusion, thrombus formation resulting in stroke and arterial embolism, pericardial effusion, and ventricular wall rupture [2,8]. Overall, in-hospital mortality has been reported in 2%−7% of TTS patients, and 30-day mortality is comparable to non−ST-segment and ST-segment elevation myocardial infarction [3−7,16,18]. Secondary forms of TTS triggered by physical stress and occurring in patients already hospitalized for another serious medical condition are associated with an even higher mortality rate ranging from 10% to 21% [12,18,19].

The pathophysiology of TTS is still incompletely understood. Microvascular dysfunction and multivessel coronary artery spasm have been proposed as the

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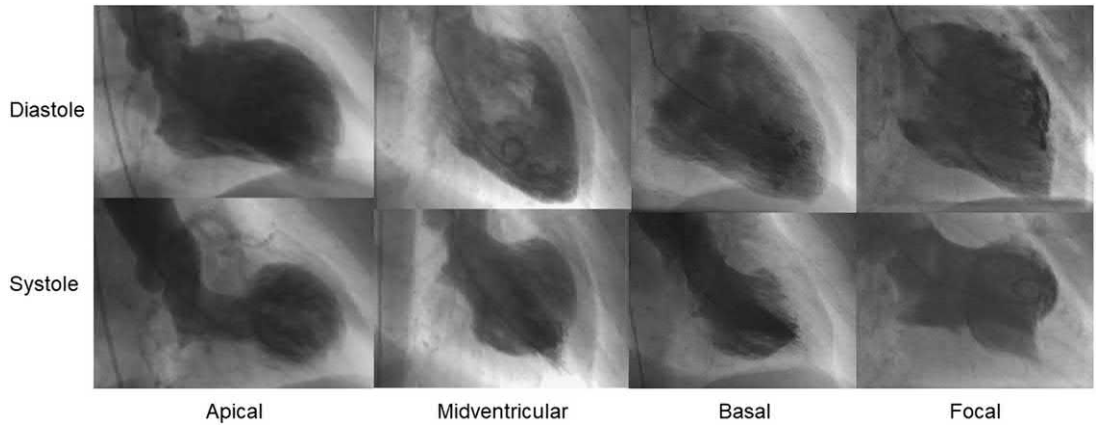

FIGURE 35.1 Wall motion patterns in takotsubo syndrome. Left ventricular angiograms in end-diastole (upper row) and end-systole (lower row) in 30 degrees right anterior oblique view demonstrating apical, midventricular, basal, and focal anterior subtype of Takotsubo syndrome.

underlying mechanism [1,9,14,20]. The most widely accepted pathogenetic mechanism is an acute stress-induced catecholamine surge with a rise in circulating epinephrine and norepinephrine from the adrenal medulla [21,22] and an increase in norepinephrine released locally from sympathetic nerves [23]. The catecholamine surge results in direct and indirect myocardial damage by inducing calcium overload, increased oxidative stress, mitochondrial dysfunction, epicardial vasospasm, and/or microvascular dysfunction leading to catecholaminergic or combined catecholaminergic and ischemic myocardial stunning [24]. Estrogen reduces β1 and β2 adrenoreceptor expression and responsiveness, and after menopause activation of β1 and β2 adrenoreceptors results in a greater response. In addition, menopause is associated with age-related worsening of microvascular dysfunction which both may predispose women to develop TTS. However, TTS occurred also in elderly women under hormone replacement therapy [12].

Myocardial biopsies taken during the acute phase of TTS have shown a myocardial inflammatory response [22,25,26]. Inflammation has also been implicated from cardiac magnetic resonance imaging (CMRI) demonstrating intense myocardial edema on T2-weighted images [27,28] which may persist for months [28]. Chronic non-resolving myocardial inflammation may in part explain persistent clinical symptoms and long-term structural and functional changes observed in a subset of TTS patients [26,29].

This chapter summarizes the electrophysiological aspects of TTS focusing on ECG findings and the occurrence of arrhythmias.

Electrocardiogram

A variety of ECG changes have been described in TTS. The ECG features are dynamic and show an evolutionary pattern over time [5,30–33]. A typical sequence during the acute and subacute phase includes (1) ST-segment elevation or depression during the first 12–24 h; (2) transient Q waves and marked QT-interval prolongation; (3) widespread T-wave inversion in precordial leads with deep negative T waves; and (4) recovery and normalization of QT interval and T-wave morphology. However, the ECG in TTS may vary widely according to the time from symptom onset, patient characteristics, wall motion abnormalities, triggers involved, race, and sex. Addressing each component of the ECG trace the following changes have been described.

PR segment

Depression of the PR segment >0.05 mV, a typical finding in the early phase of acute pericarditis, has been reported in up to 63% of patients with TTS on the admission ECG (Fig. 35.2A) [34,35]. Since by CMRI only 19% of these patients showed any sign of pericarditis or pericardial effusion, PR-segment depression in TTS was explained by the effects of the catecholamine storm on atrial repolarization [34].

Q wave

Pathologic Q waves on the admission ECG (>0.04 ms in duration and/or >25% of the following R wave in depth, QS complexes in leads V2 and V3) have been described in 10%–27% of all patients with TTS [5,9,31–34,36] and in up to 44% of those patients presenting with ST-segment elevation [30,31]. The Q waves most frequently occur in leads V2 and V3 (Fig. 35.2A and B) and are transient with resolution over the following days in parallel to reappearance of the R wave [5,31]. By 1 month after presentation, complete resolution of pathologic Q waves has been documented [32]. The presence of Q waves on the

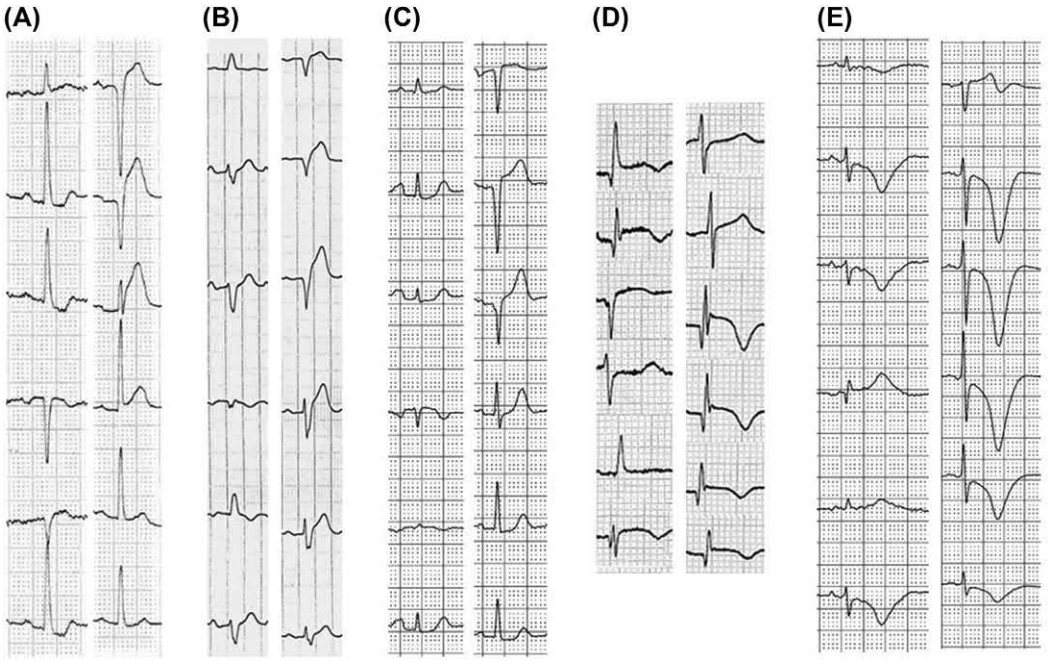

FIGURE 35.2 Electrocardiographic changes in the acute and subacute phase of takotsubo syndrome. (A) ST-segment elevation in the precordial leads, PR-segment depression and reciprocal ST-segment depression in the inferior leads. (B) ST-segment elevation in the precordial and inferior leads, QS complexes in V2 and V3. (C) Low voltage QRS complexes in all limb leads, ST-segment elevation and QS complexes in V2 and V3. (D) J waves in leads II, V3−V5. (E) QT prolongation and T-wave inversion in limb and precordial leads.

admission ECG is an independent predictor of complications in the clinical course of the disease [8]. In TTS, pathologic Q waves are unrelated to significant myocardial necrosis as demonstrated by the absence of late gadolinium enhancement on CMRI [31]. The rapid appearance and disappearance of Q waves in TTS have been explained by electrical stunning of the apex with predominant forces of the basal hyperkinetic left ventricle shifting the electrical forces upward, thereby forming Q waves in leads V2 to V4 [37].

QRS complex

Various changes of the QRS complex may be observed during the acute phase of TTS.

Low QRS voltage and amplitude attenuation of the QRS complex: Low voltage QRS complexes defined as QRS total amplitude of ≤5 mm in limb leads or ≤10 mm in precordial leads have been described in up to 91.5% of TTS patients on the admission ECG (Fig. 35.2C) [33,38,39]. The QRS amplitude shows a time-related course with an initial decrease followed by a progressive recovery of the QRS amplitude up to preevent levels [39]. A 20% increase of the QRS amplitude compared to the admission ECG has been associated with normalization of troponin and CK-MB levels and recovery of LV systolic function [39]. The transient reduction of the QRS amplitude has been related to myocardial edema and transient fibrosis, a typical feature of TTS, increasing the transmural and longitudinal inhomogeneity of ventricular depolarization and repolarization [39].

QRS prolongation: In 11% of Japanese patients, a prolongation of the QRS complex ≥120 ms on the admission ECG has been reported consisting mainly of nonspecific intraventricular conduction disturbances. -Critical complications including ventricular arrhythmias, circulatory failure, and all-cause death occurred more frequently in patients with QRS prolongation compared to those without [40]. A right or left bundle branch block on admission has been documented in 2%−6.5% and 4%−7.9%, respectively [6,40,41]. A QRS duration of >110 ms was a predictor of both in-hospital and cardiac death [40], and a QRS duration >105 ms independently predicted life-threatening arrhythmias in a French study [41]. Prolongation of the QRS complex in TTS is a transient phenomenon, normalization of QRS duration occurred in 85% of the patients until hospital discharge. The majority of patients with persistent QRS prolongation died in-hospital [40]. In TTS, QRS prolongation has been attributed to myocardial inflammation as well as ischemia due to microvascular dysfunction [40,41].

Fragmented QRS: A fragmented QRS complex with an additional R wave, notching of the R wave or notching of the S wave in two contiguous leads, has been observed in 9%−16% of patients during the hyperacute phase of TTS [33,42]. QRS fragmentation was associated with a lower

LV ejection fraction and a higher CK-MB level indicating severe myocardial damage [42]. The fragmented QRS complex is a transient phenomenon diminishing in size and amplitude within 24 h of symptom onset. The mechanism of fragmented QRS formation has been explained by both myocardial ischemia and damaged myocardium resulting in delayed and inhomogenous activation of different parts of the ventricle [42].

J wave

J waves, defined as an elevation of the QRS-ST junction ≥1 mm either as QRS slurring or notching, are a hyperacute sign of TTS with a prevalence of 16%−26% on the admission ECG (Fig. 35.2D) [33,34,42]. The appearance of J waves in TTS was also associated with a lower LV ejection fraction and a higher CK-MB level and proved to be a predictor of cardiac death and/or ventricular arrhythmias [42]. The electrophysiologic mechanism of J waves in TTS has not been studied; however, it is assumed that ischemia generates J waves by a transmural voltage gradient in the early phase of the myocardial action potential resulting from accentuation of the phase 1 notch in the epicardial but not in the endocardial layers. [34i] Within 24 h of symptom onset all J waves disappear [42].

ST segment

ST-segment elevation: The most frequently encountered finding on the admission ECG is ST-segment elevation in the precordial leads which has been documented in 44%−90% of the patients (Fig. 35.2A−D) [3,6,7,9−11,32,33,43]. ST-segment elevation is predominantly seen in leads V2−V4 but may be present also in the inferior leads in 11%−50% of the patients [15,33,36]. Over the following days, ST-segment elevation resolves [5,33,43] but may persist for ≥48 h from admission in 19% of the patients [5,43]. Persistent ST-segment elevation was associated with higher troponin levels on admission and has been identified as an independent predictor of in-hospital complications as well as major adverse cardiac events during follow-up [43]. As main complications related to persistent ST-segment elevation, LV thrombus formation and myocardial rupture have been described [8,43,44]. Persistence of ST-segment elevation may be due to ongoing sympathetic activation with prolonged microvascular constriction and myocardial stunning [43].

ST-segment depression: Reciprocal ST-segment depression has been observed in 8%−26% of the patients on the admission ECG (Fig. 35.2A and C) [32−34,36,45,46]. ST-segment depression usually involves the inferior leads in patients with precordial ST-segment elevation.

QT interval

Striking features of TTS are repolarization abnormalities with transient QT-interval prolongation and T-wave inversion developing over the first 72 h following presentation (Fig. 35.2E) [8,15,30,47−51]. Studies reporting ECG changes in TTS used a wide variation of definitions for prolongation of the corrected QT interval according to Bazett's formula, with a QTc ranging from >430 to >480 ms, and not all studies applied different cut-off values for women and men. In around 48%−67% of the patients with TTS, a slightly prolonged QTc interval is present on admission [6,11,30,33,52]. The QTc interval then increases, reaches its peak on the third day of hospitalization [5,47,48,51], and slowly decreases during the following days. More than 80% of TTS patients show a prolonged QTc interval at some point during their hospital stay [32,53], with 17%−18% of patients taking potential QT-prolonging medication [6,32]. The presence of LV hypertrophy is associated with a more pronounced QTc prolongation both in TTS and pheochromocytoma [54]. In parallel to QTc-interval prolongation, QT dispersion is also significantly increased in this acquired long QT syndrome [15,55]. The prolongation of the QTc interval usually normalizes within 14 days from presentation [32].

Both coronary microvascular dysfunction [56] and high levels of epinephrine are known to prolong the QT interval [57]. The dynamic ECG changes in TTS coincide and correlate with the apicobasal gradient of myocardial edema assessed by CMRI. The interstitial edema creates regional and transmural repolarization inhomogeneities which result in T-wave inversion and prolongation of the QT interval [49,50]. Myocardial inflammation associated with TTS may contribute to QTc prolongation [58].

T wave

Widespread T-wave inversion is another hallmark of TTS. On admission, inverted T waves have been observed in 40%−68% of the patients [5,6,36,45,51], and more than 90% show inverted T waves on day 3 after symptom onset [5,49,51]. T-wave inversion in TTS usually involves a great number of leads, most frequently leads V2 to V6, but may also be present in the limb leads. In studies from Japan two different phases of T-wave inversion have been described in up to 69% of the patients [30,47]. Inverted T waves deepened progressively with a first negative peak occurring on day 3. Then T-wave inversion improved transiently for several days with a second negative peak occurring 2−3 weeks after symptom onset [30,47]. Giant negative T waves ≥ 1 mV in the precordial leads have been documented in 21%−56% of the patients in the subacute phase of TTS [30,59] and are associated with apical wall

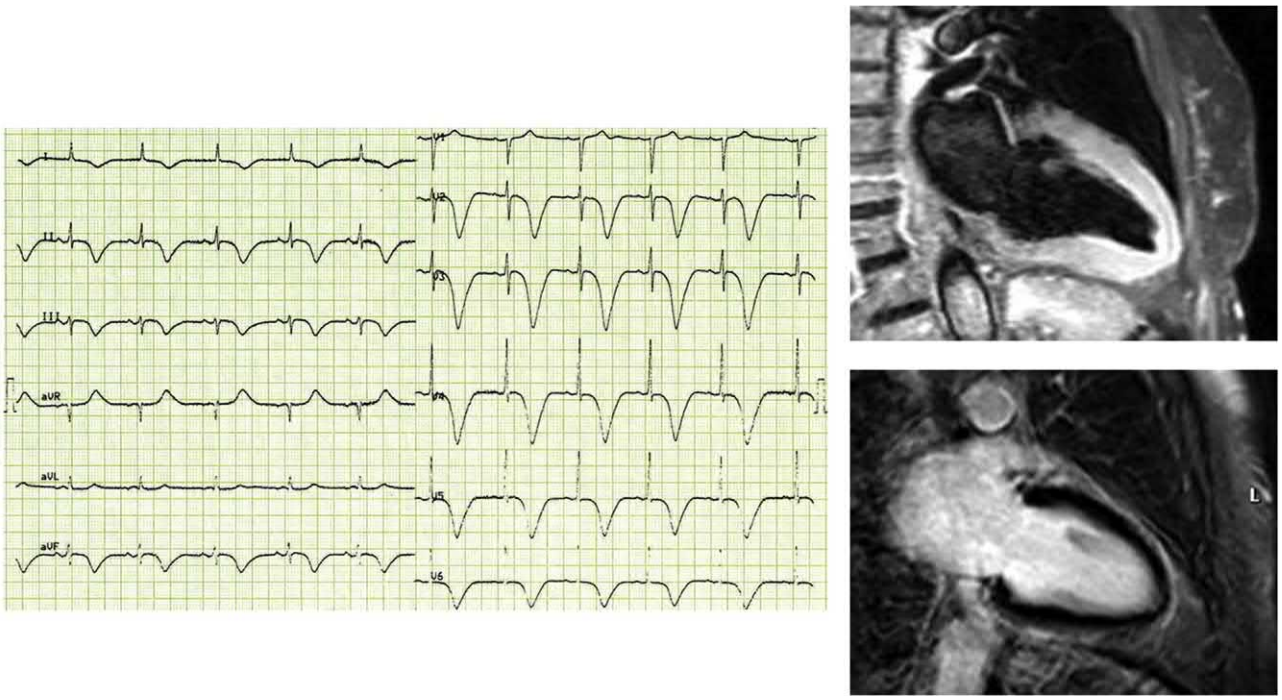

FIGURE 35.3 Giant negative T waves in takotsubo syndrome. ECG on day 5 after symptom onset with giant negative T waves in lead V2−V5 (left panel). Cardiac magnetic resonance imaging (2-chamber view, right panel): T2-weighted image showing apical edema (upper row) and absence of late gadolinium enhancement (lower row) in the apical area of the left ventricle.

thickening due to myocardial edema as demonstrated by both echocardiography and CMRI (Fig. 35.3) [59]. Tpeak-Tend (interval from the peak to the end of the T wave) as well as Tpeak-Tend dispersion are also significantly increased [15,55]. These alterations of the spatial dispersion of ventricular repolarization are more pronounced in TTS patients experiencing ventricular tachyarrhythmias [60]. The number of negative T waves and the depth of T-wave inversion decrease progressively over weeks and finally return to baseline within 2−4 months of follow-up [15,30,46,47,49,61]. In a limited number of patients residual T-wave abnormalities may be present up to 12 months after the initial event [32]. In all patients, LV ejection fraction recovers weeks before normalization of the ECG changes [15,47,49,59].

As evidenced by CMRI, the ECG pattern with dynamic negative T waves and reversible QT prolongation coincides and quantitatively correlates with the apicobasal gradient of myocardial edema and reflects the edema-induced transient inhomogeneity and dispersion of ventricular repolarization [49,50].

ECG changes according to ballooning type

In apical ballooning, ECG changes are much more pronounced than in midventricular ballooning (Fig. 35.4). On the admission ECG, ST-segment elevation was found more

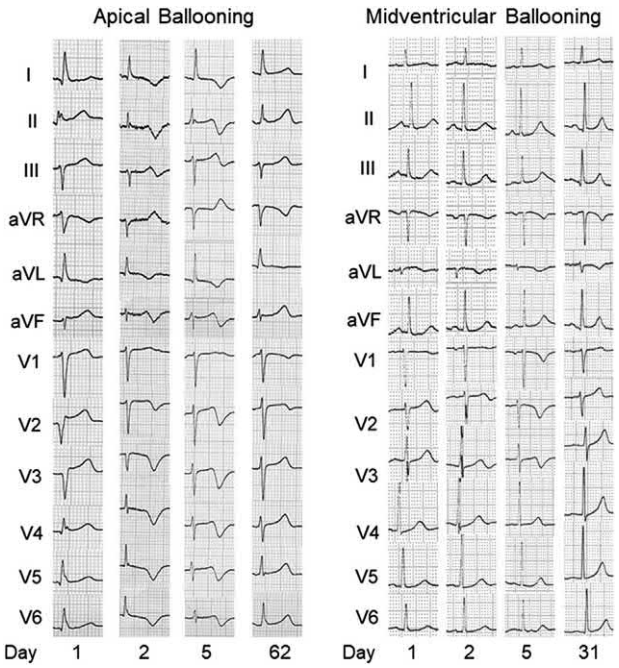

FIGURE 35.4 ECG features according to the morphological subtype of takotsubo syndrome. Apical ballooning (left panel) shows more pronounced ST-segment elevation and T-wave inversion, and time to ECG normalization is longer than in midventricular ballooning (right panel).

frequently in the apical variant and ST-segment depression was more prevalent in the midventricular type [62,63]. The sum of ST-segment elevation and the number of leads showing ST-segment elevation was significantly larger [64], and the number of leads displaying abnormal Q waves was higher in apical ballooning [46]. During follow-up, both the prevalence and the extent of T-wave inversion are significantly higher in the apical variant displaying more leads with T-wave inversion and a greater sum of T-wave inversion [46,62,64]. The QTc interval is similar in apical and midventricular ballooning [32,46,62–64], but time to complete normalization of the ECG is significantly longer in the apical variant [46]. The basal TTS subtype showed more ST-segment depression, a longer QTc interval and less T-wave inversion [11,63].

Sex differences

In Japanese studies comparing ECG changes in male and female patients with TTS ST-segment elevation on the admission ECG was found less frequently in men and was explained by a presumably later diagnosis of TTS in males [4,7]. This is in contrast to studies from Western countries either reporting no significant difference or a trend toward a higher number of male patients with ST-segment elevation despite a similar prehospital delay [5,65]. Other ECG parameters (heart rate, ST-segment depression, Q-wave or T-wave inversion) were not different among females and males [4–7,12,65]. Prolongation of the QTc interval on admission was found to be more prevalent in male patients [6,7]. Most studies found no significant difference in mean QTc-interval duration in both sexes [5,6,12,32,52], only in one study with a limited number of patients a longer QTc interval has been reported in men and was associated with the presence of LV hypertrophy [54]. The mean QTc interval peaked 3–6 h after symptom onset in males and reached its maximum 12–24 h after symptom onset in females [32]. Since women normally have a longer QTc interval than men, there may be a disproportionate QTc prolongation in male patients early in the course of TTS predisposing them to ventricular arrhythmias.

Ethnic differences

ECG features in TTS may also differ according to race. Asian patients more frequently display ST-segment elevation on the admission ECG [7,9,11,66,67], whereas T-wave inversion is more common in Caucasians [5,51,66,67]. African-American patients with TTS presented more frequently with diffuse T-wave inversion in both limb and precordial leads and a longer QTc interval, whereas Caucasians more often had ST-segment depression on admission and negative T waves limited to the precordial leads [68].

Differential diagnosis between TTS and acute coronary syndrome

Many attempts have been made to differentiate ST-elevation myocardial infarction from TTS in order to select the appropriate treatment strategy, with numerous ECG criteria proposed in the literature. However, most studies evaluating ECG findings in TTS versus anterior myocardial infarction (AMI) included only a limited number of patients, some studies compared postmenopausal women with TTS and middle-aged men with anterior AMI, or they collected only patients with either proximal or middistal occlusion of the left anterior descending coronary artery. Moreover, the definition for ST-segment elevation varied since measurements were performed at the J point in some studies or 80 ms from the J point in other studies which may affect the presence or absence of ST-segment elevation [36,69]. In addition, most studies focused only on TTS patients with ST-segment elevation, those with an apical ballooning pattern or presentation within the first hours after symptom onset. None of the previously described ECG criteria were able to definitely discriminate between TTS and AMI [45,69–72]. Since patients with TTS present with diverse and time-dependent ECG findings and no single pattern alone can be used to reliably distinguish this condition from ACS, TTS remains a diagnosis of exclusion and coronary angiography is mandatory to establish the diagnosis of TTS with certainty.

Arrhythmias in takotsubo syndrome

Arrhythmias are common in the acute phase of TTS, occurring in 20%–26% of the patients [8,9,73] They are associated with a substantial risk of severe complications and short- as well as long-term mortality [41,53,74]. Various mechanisms involving electrophysiological substrate modification, reentry, triggered activity, and abnormal automaticity have been proposed contributing to electrical instability in TTS [Moeller].

Sinus tachycardia

In patients with TTS, heart rate on admission is significantly higher than in patients with AMI [6,45,76]. A heart rate >94 beats per minute in TTS patients with sinus rhythm was associated with an increased risk of in-hospital complications [8,77,78] and all-cause mortality [78].

In TTS, the high resting heart rate on admission may reflect a positive chronotropic effect of the stress-induced catecholamine excess. Since patients with an elevated heart rate more frequently had a physical trigger, a lower LV ejection fraction [77,78], elevated inflammatory markers, and a higher prevalence of cardiogenic shock [78],

sinus tachycardia may well be an adaptive response to preserve cardiac output and compensate for a more pronounced cardiac dysfunction.

Atrial fibrillation

Atrial fibrillation (AF) of new onset may occur in 7%−25% of patients with TTS, mostly in elderly females with a high-risk profile for AF. The LV angiogram usually shows an apical ballooning pattern and a significantly lower LV ejection fraction. In TTS patients with AF or atrial flutter, a higher incidence of cardiogenic shock and an increased in-hospital, 30-day as well as long-term mortality have been reported [3,6,8,41,73,79,80]. In the majority of patients, new onset of AF is observed within the first 3 days after symptom onset [8]. The recurrence rate of AF in TTS patients during follow-up is low (11%) [53].

In TTS, acute LV dysfunction with elevated end-diastolic pressure and/or mitral regurgitation results in left atrial pressure and volume overload which may trigger AF. High catecholamine levels affecting the atrial myocardium may lead to electrical instability [81] and transient left atrial dysfunction which recovers during follow-up [82]. Additionally, inflammation may contribute to the initiation and perpetuation of atrial arrhythmias. In TTS, elevated levels of inflammatory markers were associated with the onset of atrial arrhythmias, in-hospital mortality, and cardiovascular death [41].

Sustained and nonsustained ventricular tachycardia

Life-threatening ventricular arrhythmias during the acute phase of TTS have been reported in 4%−9% of the patients and are associated with younger age, male sex, lower LV ejection fraction, higher troponin levels, QRS duration >105 ms, J waves, and prolongation of the QTc interval >510 ms [8,9,40,41,48,73,74]. Ventricular arrhythmias typically develop within the first 3 days of presentation when the QTc interval is longest (Fig. 35.5) [8,83,84]. Pause-dependent polymorphic ventricular tachycardia (VT) (torsades de pointes, TdP) with degeneration into ventricular fibrillation is the most common manifestation (Fig. 35.6) [48,50]. Monomorphic VT due to a reentry mechanism has also been observed in a substantial number of patients [50,74]. Since male patients with TTS may have a more pronounced QT-interval prolongation due to a higher LV mass [54] with an early peak of the QT interval 3−6 h after symptom onset [32], they may be more susceptible to develop torsades de pointes tachycardia than women early in the course of TTS [85].

Epinephrine release, inflammation, myocardial edema, ischemia, oxidative stress, and low estrogen hormone levels were proposed as important mechanisms involved in QT prolongation and T-wave inversion in TTS. The epinephrine surge increases automaticity, action potential duration, QT interval, and QT dispersion and induces early and delayed afterdepolarization. Myocardial edema and inflammation increase the transmural dispersion of repolarization. All these mechanisms may result in abnormal automaticity, triggered activity, and cardiac reentry contributing to the onset of ventricular arrhythmias in TTS.

Sinoatrial block

Sinoatrial block occurring in the context of TTS is rare and has been reported in 0.9%−1.4% of the patients, with almost half of them receiving a permanent pacemaker [41,74].

Atrioventricular block

New onset of second- or third-degree atrioventricular (AV) block has been reported in 2.8%−4.5% of patients in the acute and subacute phase of TTS, particularly in those over 70 years of age. The AV block occurs within 3 days after symptom onset [8] and may be transient lasting for a few days, persistent for months or even permanent [8,9,41,50,74]. With normalization of LV function, the AV block may resolve over a period of 2−3 weeks [86,87]. However, in a substantial number of TTS patients, the conduction delay persists despite complete recovery of LV ejection fraction and permanent pacemaker implantation is required [41,74].

Catecholamine excess with increased vagal tone and reflex bradycardia may explain the occurrence of an AV block in the acute setting [88]. In the context of severe prolongation of the QTc interval, a functional 2:1 AV block has been observed which was fully reversible after regression of the QTc interval [50]. Myocardial edema also contributes to conduction disturbances in TTS including complete AV block, sinoatrial block, or transient pacing failure [89]. The persistence of conduction disturbances together with the high rate of ventricular pacing in TTS patients requiring pacemaker implantation points to a particular sensitivity of conduction fibers to edema, inflammation, and ischemia [41].

Cardiac arrest

Cardiac arrest has been reported in 4%−10% of the patients with TTS, occurring during the first 3 days after symptom onset [5,41,48,73,74,83,90]. Compared to TTS patients without cardiac arrest, those experiencing cardiac arrest were younger, more frequently male, had physical triggers, an apical ballooning type, a lower ejection fraction, AF, and a longer QT interval [90]. Cardiac arrest may have various causes such as TTS-related hypotension, pulseless electrical

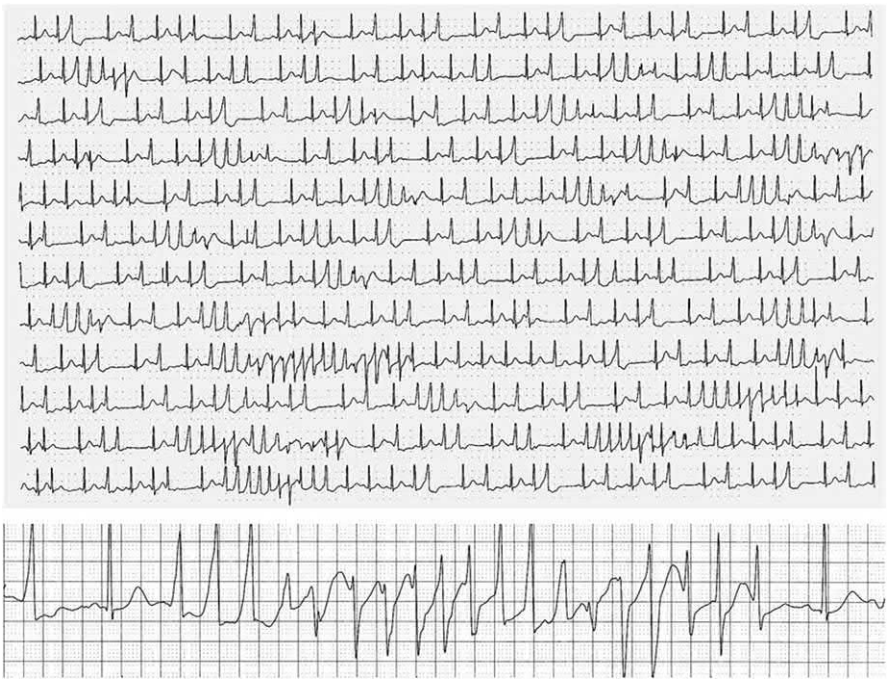

FIGURE 35.5 ECG monitoring with recurrent Torsades de Pointes Tachycardia. On day 3 after symptom onset, the patient experienced repetitive episodes of polymorphic ventricular tachycardia.

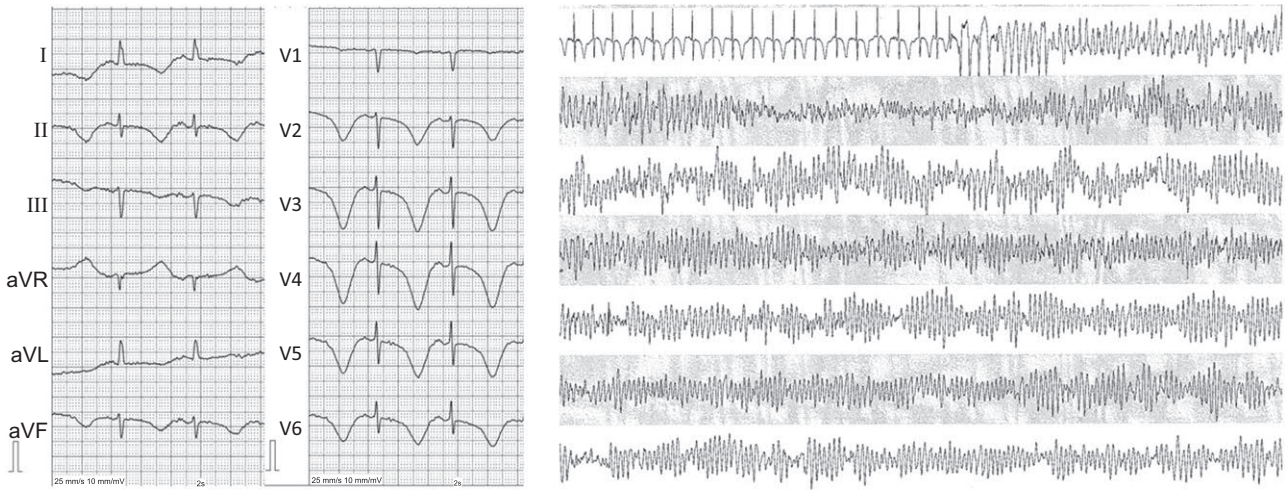

FIGURE 35.6 Acquired long QT syndrome with polymorphic ventricular tachycardia. ECG with prolongation of the QT interval (left panel) and TdP eventually degenerating into ventricular fibrillation (right panel).

activity, asystole, complete AV block, sinoatrial block, VT, or ventricular fibrillation [73,83,90]. The occurrence of cardiac arrest is associated with a higher short- as well as long-term mortality [90].

Electrophysiologic studies in TTS

There are a number of case reports of TTS following an electrophysiologic study with infusion of epinephrine or radiofrequency catheter ablation of AF, AV node, or the right ventricular outflow tract [91–95]. As potential mechanisms triggering TTS in this context, emotional and physical stress associated with the procedure, damage of the autonomic plexi located in the antrum of the pulmonary veins, administration of catecholamines during catheter ablation, or increased sympathetic nerve activity after AV node ablation have been discussed.

Electrophysiologic studies for the evaluation of TTS-related arrhythmias have been performed in a limited number of patients. With respect to AV conduction disturbances, a complete AV block may be of supra-Hisian, intra-Hisian, or infra-Hisian origin. In cases with early resolution of the AV block, no conduction abnormalities have been identified (Table 35.1) [87,96–99].

TABLE 35.1 Electrophysiologic studies in patients with Takotsubo syndrome.

References	Patient characteristics	Arrhythmia	Management	Electrophysiologic study
Inoue et al. [96]	82 y, F, apical type	Complete AV block, TdP	Temporary transvenous pacing Pacemaker on day 18 Persistent AV block at 3 months	Intra-Hisian block
Nault et al. [97]	62 y, F	Complete AV block and 2:1 AV block	VDD pacemaker Persisting AV block at 1 year AV conduction normal after 2 years	Infra-Hisian block
Benouda et al. [98]	68 y, F, apical type	2:1 AV block, stress test with complete AV block	DDD pacemaker after 9 months Permanent AV block at 2 years	EPS on day 10 Intra-Hisian block
Sugiura et al. [99]	63, F, midventricular type	Complete AV block	Temporary transvenous pacing Normal AV conduction on day 3	EPS on day 13 Normal AH and HV interval
Prabhu et al. [87]	66 y, F, apical type	2:1 AV block, transient complete AV block 2:1 AV block at 2 weeks	Temporary transvenous pacing VVI pacemaker on day 17 Normal AV conduction at 1 month	EPS on day 2 Supra-Hisian block
Imori et al. [100]	77 y, F, apical type LV + RV	Sinus arrest, wide QRS escape rhythm	Temporary transvenous pacing Sinus rhythm at 2 weeks	Sinus node and AV node function "almost normal"
Akashi et al. [101]	67 y, F, apical type	Polymorphic VT/TdP	ICD implantation, no discharge for > 10 years	Normal AV conduction No inducible ventricular arrhythmias
Konety et al. [102]	71 y, F, apical type with LVOTO and MR	Nonsustained VT after 6 weeks, LV normalized	Implantable loop recorder with no further arrhythmic episodes	No inducible ventricular or supraventricular arrhythmias despite isoproterenol
Furushima et al. [103]	61 y, F, apical type	Polymorphic VT/TdP QTc 740 ms	Temporary transvenous pacing, mexiletine ICD implantation, no discharge at 6 months	Ventricular repolarization gradients increasing from basal to apical LV site and from endocardium to epicardium

AV, atrioventricular; *F*, female; *ICD*, implantable cardioverter/defibrillator; *LV*, left ventricle; *LVOTO*, left ventricular outflow tract obstruction; *MR*, mitral regurgitation; *RV*, right ventricle; *TdP*, torsades de pointes; *VT*, ventricular tachycardia.

In patients with polymorphic or monomorphic VT during the acute and subacute phase of TTS, there were no inducible ventricular or supraventricular arrhythmias in the electrophysiologic study despite administration of isoproterenol [101–103].

Therapeutic considerations in TTS-associated arrhythmias

Currently, there is no specific evidence to guide treatment decisions in TTS patients from prospective randomized trials. Knowledge is mostly derived from clinical experience, single-case reports, observational studies, or TTS registries. Since a typical feature of TTS is the recovery of cardiac function over days to weeks, the treatment strategy is mainly supportive in order to minimize life-threatening complications [2]. Given the substantial risk of complications, all patients with confirmed TTS should have continuous ECG monitoring for at least 24 h including periodic assessment of the QTc interval on the resting 12-lead ECG [2]. The ECG may help to risk stratify TTS patients since sinus tachycardia >94 bpm on admission, AF, Q waves, QRS prolongation >105 ms, or a J wave and persisting ST-segment elevation >48 h and QTc prolongation >510 ms may identify patients at increased risk for complications. Patients at higher risk should be monitored for a prolonged time period (minimum 72 h from presentation) [2,8]. Based on the pathophysiology of catecholamine toxicity causing TTS, sympathomimetic drugs should be avoided and beta-blockers seem to be a reasonable treatment option. However, in view of the potential risks of conduction disorders and pause-dependent TdP, beta-blockers should be used cautiously, especially in TTS patients with bradycardia or severe QT prolongation [48,74].

All TTS patients with AF or atrial flutter should receive therapeutic anticoagulation according to the guidelines for AF. Rate control may be achieved by a beta-blocker, preferably a short-acting drug in order to avoid bradycardia. Digoxin, calcium antagonists, and QT-prolonging agents such as amiodarone and sotalol should generally be avoided in patients with TTS. In patients with a high heart rate and hemodynamic compromise, electrical cardioversion may be considered after exclusion of intracardiac thrombi by transesophageal echocardiography.

Since most ventricular arrhythmias occur within 3 days of symptom onset, close ECG monitoring should be performed in the high-risk patients for at least 72 h. All drugs potentially prolonging the QTc interval (antidepressants, antibiotics) should be stopped immediately. Intravenous magnesium and supplementation of potassium have been successfully used in QTc prolongation and TdP [48,75]. In patients with normal or high heart rate, a short-acting beta-blocker can be helpful to suppress ventricular arrhythmias. However, if pause-dependent TdP occurs, beta-blocker therapy should be withheld and instituted only after bradycardia and QT-interval prolongation have normalized. In TTS cases with bradycardia and pause-dependent TdP overdrive stimulation with temporary transvenous pacing may be effective [41,48,74]. Antiarrhythmic drugs which have been used in TTS are mexiletine, lidocaine, and amiodarone. However, all class III antiarrhythmic agents such as amiodarone or sotalol should generally be avoided since they may further prolong the QTc interval. Cardiac arrest after hospital admission due to polymorphic VT or ventricular fibrillation requires external defibrillation. Ventricular arrhythmias in TTS are limited to the acute phase, with both QTc prolongation as well as LV dysfunction reversible; therefore, routine implantation of a cardioverter defibrillator is not required. In TTS patients who received an ICD after resuscitation and/or torsades de pointes, no ventricular arrhythmias have been documented during a follow-up period of up to 71 months [8,41,48,74,86]. A wearable external cardioverter/defibrillator vest may be considered in patients with excessive and/or slowly resolving QTc prolongation until QTc interval and LV function have normalized or if an inherited long QT syndrome unmasked by TTS is suspected until the results of genetic testing are available [104].

High-degree AV block observed in a small number of TTS patients during the acute phase should be treated with temporary transvenous pacing until the AV block resolves. However, the AV block may persist for months or can be permanent requiring pacemaker implantation in a substantial proportion of patients [41,50,74]. Preexisting AV conduction disturbance in patients of advanced age [50] as well as persistent long-term structural changes as a consequence of TTS [29] may be responsible for a permanent AV block in these patients.

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Part X

Supraventricular tachycardias

Chapter 36

Sex and cardiac electrophysiology: supraventricular ectopies

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Supraventricular premature beats (SVPBs) are atrial contractions arising in ectopic foci rather than in the sinoatrial node. SVPBs are found in healthy individuals or in patients with underlying heart disease and can be asymptomatic or felt as palpitations. External triggers (alcohol, caffeine, smoking, stress) and several disease conditions (arterial hypertension, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, thyroid malfunction, electrolyte imbalances, or drug toxicity) may favor SVPB occurrence. SVPBs increase with age and are slightly more common in males than in females. SVPBs are generally a benign condition; however, frequent SVPBs may beget prolonged repolarization, atrial fibrillation, or even ventricular tachycardia and, rarely, ventricular fibrillation. Asymptomatic SVPBs without underlying structural heart defects generally do not require treatment, while the concomitant disease conditions should be treated, and potential external triggers should be avoided. β-Blockers, calcium antagonists, class 1c antiarrhythmic drugs or amiodarone, or radiofrequency catheter ablation can be used in selected patients with persistent symptoms.

Introduction

Supraventricular premature beats (SVPBs) are atrial contractions arising in ectopic foci rather than the sinoatrial node. SVPBs can arise in different areas of the atrial myocardium (atrial premature beats [APBs]) or through retrograde conduction in the atrioventricular (AV) node (junctional premature beats [JPBs]). The typical ECG findings are P-wave abnormalities (or absent P waves), altered PR interval (compared to the normal beats), normal or aberrant QRS complex, and absence of full compensatory pause [1,2]. SVPBs may be found in healthy individuals as well as patients with underlying heart disease, and they can be asymptomatic or felt as palpitations. Several external triggers, such as alcohol, caffeine, smoking, and stress, as well as several disease conditions such as arterial hypertension, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea syndrome (OSAS), thyroid malfunction, electrolyte imbalances, or drug toxicity (e.g., digoxin), may contribute to exacerbate the condition [1,3–5].

SVPBs are generally a benign condition, which does not significantly impair cardiac output. However, SVPBs may lead to more severe forms of arrhythmia and, specifically, they may beget atrial fibrillation (AF) and supraventricular or even ventricular tachycardia [6–10].

Treatment for SVPBs is generally not required in asymptomatic individuals without underlying structural heart defects, while the concomitant disease conditions (e.g., electrolyte imbalance or arterial hypertension) should be treated. Symptomatic patients should be advised to reduce potential triggers such as caffeine, alcohol, stress, and smoking. β-Blockers (specifically cardioselective β1-antagonists or sotalol), calcium antagonists (verapamil or diltiazem), antiarrhythmic drugs (class 1c drugs or amiodarone), or radiofrequency catheter ablation may be used in selected patients with persistent symptoms [8].

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Age and sex prevalence of frequent SVPBs

The sex prevalence of SVPBs is unclear, while there is a clear sex-dependent difference in the incidence of the different types of paroxysmal supraventricular tachycardia, with AV nodal reentrant tachycardia and focal atrial tachycardia being more common in females and accessory pathway−mediated orthodromic AV reentrant tachycardia being more common in males [3−5].

Few studies addressed the question of the prevalence of SVPBs by age and sex. In the "Cardiovascular Health Study" carried out in a population of healthy subjects >65 years of age, the prevalence of SVPBs (defined as >15/h) was significantly higher in men than in women (28.2% vs. 18.1%, $P < .0001$) and increased with age in both sexes [5]. In the "Copenhagen Heart Study" in apparently healthy individuals aged 55−75 years, frequent SVPBs (defined as >30 SVPBs per hour or runs of >20 SVPBs) were found in 35.4% women and 42.5% of men, but these differences were not significant [6].

The cross-sectional analysis among participants of the population-based "Swiss cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA)," assessing the frequency of SVPBs in patients with age above 50 years, showed that the SVPB frequency was independently associated with age, height, history of cardiovascular disease, natriuretic peptide levels, physical activity, and high-density lipoprotein cholesterol, while sex, hypertension, and body mass index were not significantly related to SVPB frequency [1].

Although there is no clear definition of frequent SVPBs, the cutoff of >30/h appears to be a consistent risk factor. SVPB frequency increases with age, and SVPBs may be slightly more frequent in males than in females. It remains unclear if and why women experience more symptoms from SVPBs than men, but in general women with all types of paroxysmal arrhythmias are more aware of symptoms and have worse quality of life than men, mainly because of anxiety [3,4].

Site of origin of SVPBs and ECG characteristics

SVPBs result from ectopic stimuli arising from different loci outside the sinoatrial node, either in the left or right atrium, including the left atrial free wall, around the superior or inferior vena cava, and in proximity of the coronary sinus, the interatrial septum, the crista terminalis, and the pulmonary veins. After the atria are depolarized from an ectopic site, giving rise to an atrial or junctional depolarization, the stimulus may spread normally through the His-Purkinje system into the ventricles. For this reason, ventricular depolarization (QRS complex) is generally not affected by APBs or JPBs, as the stimulus may spread normally through the His-Purkinje system into the ventricles [2,3].

The site of the ectopic focus can be established accurately only using intracardiac electrodes. However, the analysis of P wave morphology on the surface ECG can be helpful for defining the source of ectopic activity [2]. This is because foci located at divergent sites can produce similar P wave patterns, and different P wave patterns can be caused by impulses originating at the same site owing to differences in intraatrial or interatrial conduction. Notwithstanding these limitations, certain correlations have been established. If the focus is near the sinus node, the premature P wave simulates the sinus P wave closely. If the focus is in the vicinity of the AV junction, the premature ectopic P wave is inverted in the inferior leads. Such P wave differs from the premature AV junctional complex, in that the PR interval is usually 120 ms (msec) or longer. Clinical correlations suggest that a negative P wave in lead I usually indicates a left atrial focus, unless it is associated with dextrocardia or dextroversion. A negative P wave in leads II, III, and aVF can signify a focus in the left atrium, coronary sinus, or low right atrium. In the right precordial leads, the normal P wave or an ectopic P wave arising near the sinus node is usually positive-negative, while the left atrial or low right atrial ectopic P wave is usually negative-positive [2,3].

The PR interval of SVPBs may be normal, shorter, or longer than in normal sinus complexes. The PR interval is usually similar to the PR interval of the basic sinus complex when the ectopic impulse appears relatively late and the ectopic pacemaker is near the SA node, while the PR becomes shorter if the focus is near the AV node. The SVPB coupling may be variable, but ectopic P wave can always be recognized, inscribed in the preceding T wave (Fig. 36.1). An early premature complex may not be conducted to the ventricles, resulting in a blocked premature atrial complex. A blocked premature atrial complex should not be mistaken for a second-degree AV block, where the P−P interval remains constant, and the P wave morphology is unchanged. Often the SVPBs may be conducted with aberrancy and may be mistaken as ventricular premature beats (Fig. 36.2).

Effects of sex hormones on cardiac repolarization and arrhythmogenesis

Sex differences in cardiac repolarization involve effects of sex hormones through differences in expression of ion channel subunits and channel function modulation [4,5,11,12]. Direct effects of sex hormones on ion channels involved in atrial and ventricular repolarization have not yet

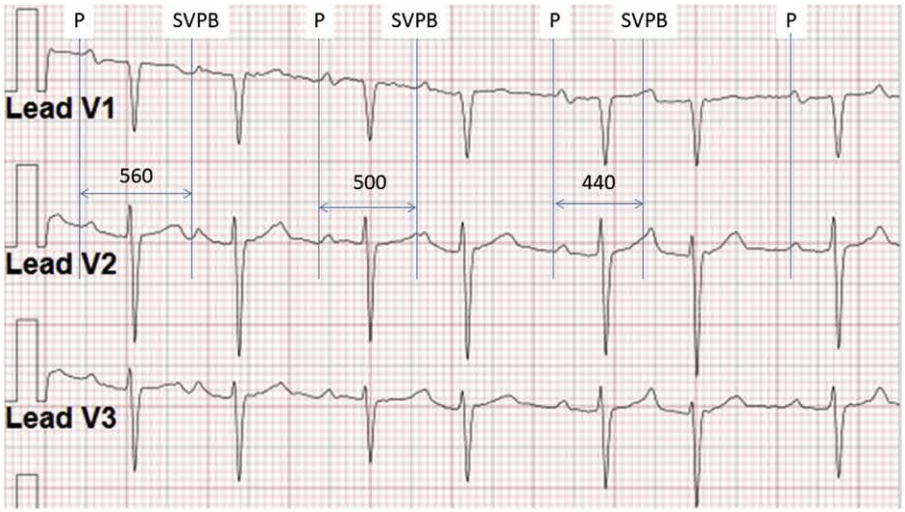

FIGURE 36.1 Supraventricular premature beats (SVPBs) with different coupling intervals in the same tracing: the P waves can always be recognized, inscribed within the preceding T waves.

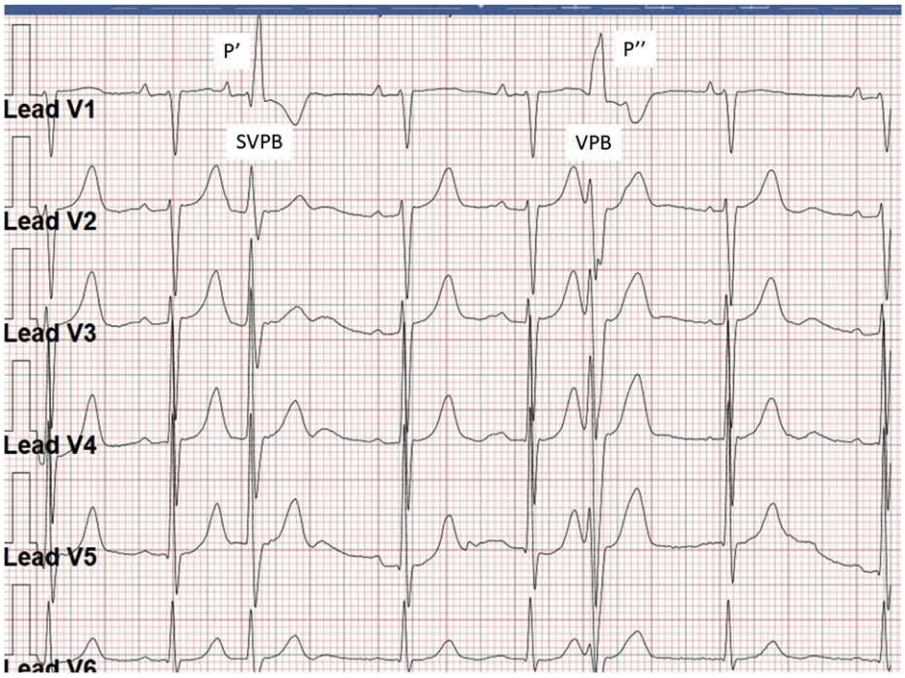

FIGURE 36.2 The supraventricular premature beat (SVPB) with aberrant conduction along the right bundle branch (BBD) is preceded by an ectopic P wave, while the subsequent ventricular premature beat (VPB, again with BBD aberrancy) is followed by a retrograde P wave.

been conclusively demonstrated, and conflicting data have often been reported [4,5].

Sex differences have been described in different species in the depolarizing sodium currents, both at atrial and ventricular levels, and regional disparities appear to be decreased by testosterone. Sex differences in excitation–contraction coupling are documented, as contractions of ventricular myocytes appear smaller and slower in female cells compared with male cells, particularly at faster pacing rates. As to myocardial repolarization, female myocytes have longer action potential duration than male myocytes paced at the same rate, and this may be because of differential influences of sex hormones on calcium currents [11].

Female hearts also have reduced expression of potassium channel subunits involved in cardiac repolarization, and sex hormones influence potassium channels differently, as estradiol inhibits IKr while in contrast, testosterone increases IKs, with possible protective arrhythmic

influence. Sex hormones may also affect the expression and function of calcium cyclic proteins involved in generating early after depolarization (EAD) and triggered activity, with female cells having increased susceptibility to EAD, because of reduced repolarization reserve, with possible higher likelihood of arrhythmias [12].

Clinical and experimental studies have shown that sex differences exist in cardiac repolarization in various animal species and human, as is evidenced by significantly longer QT, JT intervals, and action potential duration in females than in males, with higher incidence of torsade de pointes (TdP) in females favored by drugs blocking repolarizing potassium currents [11,12]. Noteworthy, atrial repolarization is important in the development of arrhythmias, and specifically of AF, but no direct measurement is available in clinical medicine. However, a prolonged QT interval, a possible indirect marker of prolonged atrial repolarization is associated with an increased risk of incident AF [13].

Relation between SVPBs and development of atrial fibrillation

The relation among frequent SVPBs and AF remains unclear, but several possibilities exist. The automaticity theory recognized a triggering focus at the level of the pulmonary veins creating a SVPB with a critical coupling necessary for the induction of AF. The multiple atrial reentry wavelet theory suggested that multiple electric activation fronts advance through the atria activating contiguous atrial tissue just after the refractory period, thus creating a vicious circle. For the AF to be sustained, a critical number of simultaneous wave fronts must be present, each dependent on a critical mass of atrial tissue. AF could be also triggered by high-frequency micro reentry localized on the atrial septum or on the left posterior atrial wall (pulmonary vein ostia).

All those different mechanisms could lead alone or in combination with the various forms of AF. In patients with paroxysmal AF, without structural heart disease and with normal sized atria, the focal pulmonary veins onset seems prevalent; in persistent AF, often part of significant structural heart diseases with chambers dilation and atrial remodeling, the reentry mechanism seems more likely [7–10,14]. Frequent SVPBs and short burst of atrial ectopic activity (defined as nonsustained supraventricular tachycardia [nsSVT] lasting less than 30 s) may precede and favor the onset of AF (Fig. 36.3).

The radiofrequency ablation of supraventricular ectopic foci was associated with a significant reduction in the occurrence of AF [15]. In patients with frequent SVPBs, novel AF high-density electroanatomical mapping techniques, simultaneously characterizing multiple arrhythmia substrates, including rapid and regular activities, wavefront conduction velocity, and fragmented and low-voltage areas, may allow an integrated visualization of the substrate and might open new possibilities for substrate-focused ablation strategies serving as a potential tool for a patient-tailored approach [16].

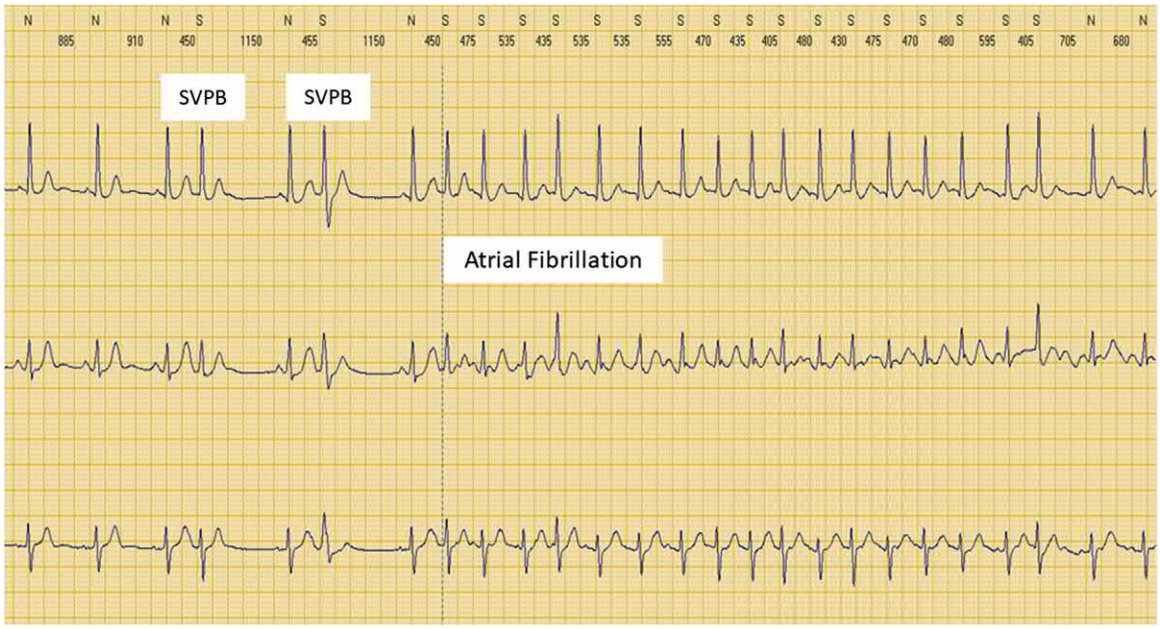

FIGURE 36.3 A supraventricular premature beat (SVPB) initiates a sequence of short-long-short cycles, which presumably modify atrial conduction and refractoriness, favoring the onset of a brief burst of atrial fibrillation (lasting 13 s) (male patient, age 54 years, history of arterial hypertension, and paroxysmal atrial fibrillation).

Frequent SVPBs and risk for atrial fibrillation and stroke

The mechanisms by which increased SVPBs may increase the risk of AF and stroke or death are not completely understood. The most likely mechanism is that increased SVPBs trigger AF or act as forerunner of atrial AF. However, it cannot be excluded that increased SVPBs and AF are epiphenomena of other heart diseases or conditions that also increase the risk of stroke or death. In the "Copenhagen Heart Study," frequent SVPBs were associated with a 2.7-fold increased rate of AF during >6 years follow-up and with a 60% increase in the rate of death or stroke after adjustment for other risk factors [7]. For each increase of 10 SVPBs per hour, the risk of the primary endpoint of death or stroke increased by 27% and the risk of AF by 50%. Subjects who developed AF during the follow-up period had significantly higher systolic blood pressure at baseline and were older. Other baseline variables and risk factors (sex, cholesterol, smoking, diabetes mellitus, alcohol, plasma glucose, and NT-proBNP) were not significantly different between the groups. In Cox regression models, SVPBs as a continuous variable and nsSVT were also significantly associated with occurrence of AF fibrillation in both univariate and age- and sex-adjusted model. Further adjustments for systolic blood pressure and body mass index did not change the results [7].

In the EMBRACE trial, among patients with previous cryptogenic stroke or transient ischemic attack (median CHADS2 score 3), multivariable logistic regression assessed the association between Holter-detected APBs, nsSVT, age, left atrial enlargement, and subsequent AF detection. Specifically, patients with AF during 30 days ECG monitoring were older and had more frequent SVPBs at baseline Holter than those without AF, but no sex-related differences were detected [10].

Frequent SVPBs and arterial hypertension and cardiac hypertrophy

Increased SVPBs may be an early manifestation of hypertension or other underlying structural heart diseases, such as hypertrophic cardiomyopathy, which elevates cardiac filling pressures. Long-standing hypertension can lead to diastolic dysfunction and enlargement of the left atrium, which can potentially lead to increased atrial wall stress, increased SVPBs, and eventually AF. Thus, patients with excessive SVPBs and left ventricular hypertrophy have a greater risk of developing nsSVT and AF (Fig. 36.4). Frequent SVPBs are associated with increased age, systolic blood pressure, and N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, while sex did not appear to be an independent risk factor [1,4–6]. Optimization of hypertension management with drugs that block the renin–angiotensin system may prevent the development of SVPBs and AF in both women and men.

SVPBs and atrial fibrillation in channelopathies

Increased SVPBs, nsSVT, and AF may be observed in several genetically determined channelopathies, and their

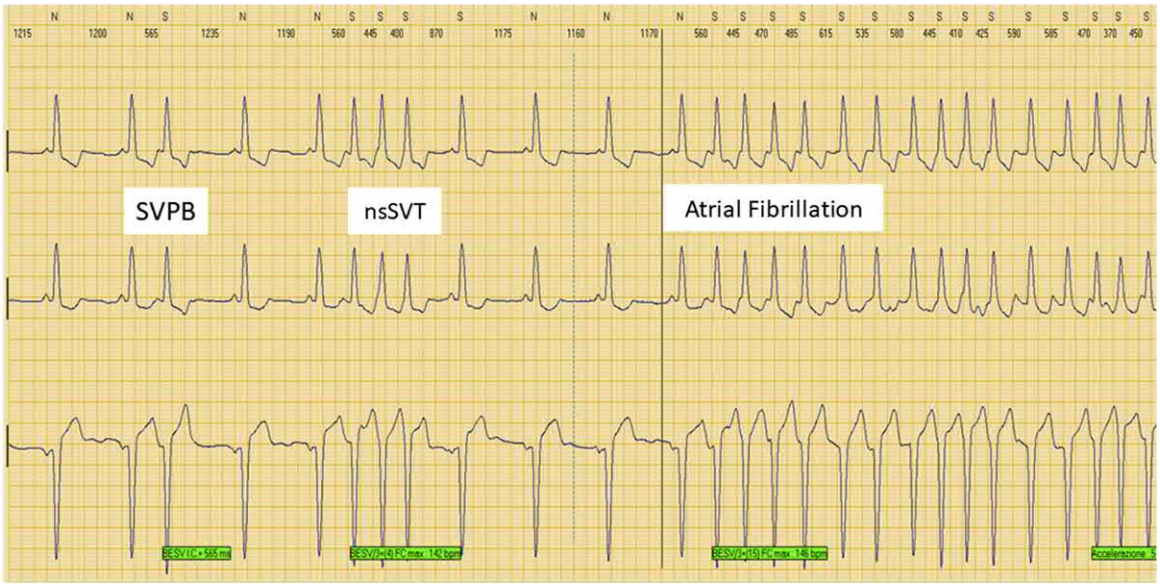

FIGURE 36.4 Series of isolated supraventricular premature beats (SVPBs) and brief burst of nonsustained supraventricular tachycardia (nsSVT) precede the onset of sustained paroxysmal atrial fibrillation (lasting 6 h) (female patient, age 68 years, history of arterial hypertension, left atrial dilatation, and hypertensive cardiac hypertrophy).

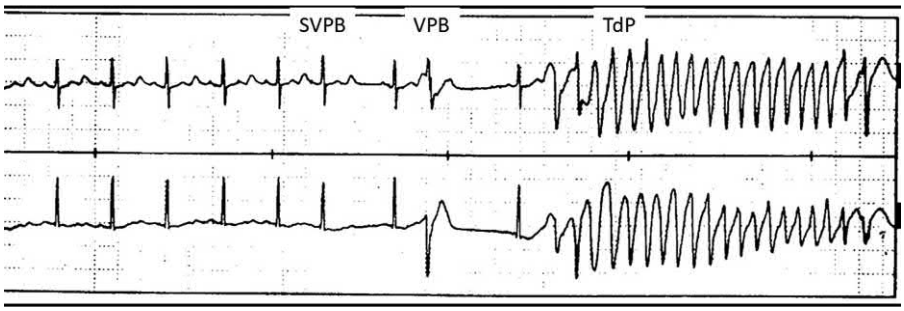

FIGURE 36.5 Example of cascade phenomenon, where a single premature atrial beat initiated a short-long phenomenon leading to the onset of a first premature ventricular beat, whose compensatory pause triggered the onset of torsade de pointes (TdP). Note the major changes in T wave configuration in the beat after the postextrasystolic pause (female patient, age 62 years, history of rheumatic valve disease, and paroxysmal atrial fibrillation, on therapy with amiodarone and diuretics, QTc 616 ms). *SVPB*, supraventricular premature beat; *VPB*, ventricular premature beat.

presence may precede the onset of ventricular arrhythmias and even ventricular fibrillation [17−19]. In patients with SCN5A gene mutations, a gene encoding the pore-forming ion-conducting α-subunit of the cardiac sodium channel (Nav1.5), responsible for the initiation and propagation of action potentials and determining cardiac excitability and conduction of electrical stimuli through the heart, several disease entities can be caused by different mutations. Gain-of-function mutations in SCN5A can lead to more sodium influx into cardiomyocytes through aberrant channel gating and can cause long QT syndrome (LQTS). Loss-of-function mutations in SCN5A lead to lower expression levels of SCN5A or production of defective Nav1.5 proteins and can cause Brugada syndrome (BrS). In patients with SCN5A-related diseases, supraventricular ectopic beats and multifocal ectopic premature Purkinje-related complexes (gain-of-function mutations), isolated cardiac conduction defect (loss-of-function mutations), sick sinus syndrome (loss-of-function mutations), AF (loss-of-function or gain-of-function mutations), and overlap syndromes (mutations with both loss-of-function and gain-of-function effects) can be observed.

In BrS, supraventricular beats and AF can be the first clinical manifestations preceding the onset of ventricular arrhythmias. Noteworthy, young patients with new onset of lone AF should be viewed with special care because they may be carriers of latent BrS and may be at risk of VF and sudden death [18]. In other channelopathies, atrial and ventricular fibrillation may develop concomitantly as a result of global atrial and ventricular vulnerability [16,18].

SVPBs, prolonged QT interval, and risk of atrial and ventricular fibrillation

A prolonged QT interval, a possible indirect marker of prolonged atrial repolarization, is known to be associated with an increased risk of incident AF [13]. In a recent study, the presence of prolonged QTc before ablation doubled the risk of AF/AT recurrence independently of other risk factors [20]. A prolongation of the QT interval can be observed in the beat following a supraventricular or ventricular ectopic beat, together with morphological alteration of the T wave [12,21−23]. This phenomenon can be amplified in patients with congenital LQTS or in patients exposed to drugs or conditions that prolong the QT interval, particularly among women [11−13,21−23] (Fig. 36.5). Therefore, an isolated supraventricular beat can initiate a so-called "short-long-short sequence," which in patients with reduced ventricular repolarization reserve may induce further prolongation of the QT interval, related to the onset of pause-dependent EADs, leading to polymorphic ventricular tachycardia or TdP [12,22,23].

Summary and conclusions

SVPBs can be observed in healthy individuals or in patients with underlying heart disease, and external triggers (alcohol, caffeine, smoking, stress) and several disease conditions (arterial hypertension, COPD, OSAS, thyroid malfunction, electrolyte imbalances, or drug toxicity) may favor their occurrence. SVPBs increase with age and are slightly more common in males than in females. SVPBs are generally a benign condition; however, frequent SVPBs may beget prolonged repolarization, AF, and even TdP and ventricular fibrillation in vulnerable patients with reduced repolarization reserve.

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Chapter 37

Sex differences in focal atrial tachycardia

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Incidence and clinical characteristics of focal atrial tachycardia

Focal atrial tachycardia (FAT) generally shows female predominance, with an incidence of 48%−62%, but the results are inconsistent [1−4]. Distinct mechanisms may underlie FAT in different atrial foci (e.g., right or left atria). In the German ablation registry [1], the incidence of right atrial foci was higher in women than in men; however, men had a higher incidence of left atrial or biatrial FAT foci [1]. In an Asian hospital cohort, the incidence of left atrial FAT was not different between women and men [2]. A number of the small ablation cohort studies reported the incidence of female patients among total population in different foci of FATs, including parahisian (72%−78%) [5,6], right atrioventricular annulus (52%) [7], right atrial appendage (10%) [8], coronary artery cusps (86%) [9], and left atrial appendage (64%) [10]. These studies were not designed for sex analysis and had the limitations of considerable heterogeneity and small sample size. Compared with men, women with FAT had more second arrhythmias, mostly atrioventricular nodal reentrant tachycardia (AVNRT, 17.0% vs. 28.9%) [2,3]. By contrast, men with FAT receiving catheter ablation had more cardiovascular comorbidities and persistent tachycardia (14.7% vs. 4.4%) [2]. In the registry of 24-h Holter monitoring data, patients with short-term FAT were generally older, were men, and had hypertension and coronary artery disease. CHA_2DS_2-VASc scores of 0 for men and 1 for women predict the future risk of stroke attack [11]. Male patients with persistent AF receiving catheter ablation had a tendency toward fewer AT recurrences than the female patients (OR: 0.60, 95% CI: 0.34−1.05, $P = .07$), although the mechanism was unclear [12].

Electrophysiological characteristics of FAT: The electrophysiological characteristics of FAT varied among different reports [4]. The sample size in each report was small, and definitions of the location and mechanism of atrial tachycardia were inconsistent [1,2,4]. Sex analysis has rarely been conducted. No sex differences were found in the FAT number and shortest tachycardia cycle [2]. The atrial effective refractory period (ERP), functional refractory period (FRP), atriohisian interval, hisian−ventricular interval, atrioventricular node (AVN) ERP, AVNFRP, ventricular ERP, and ventricular FRP also did not differ between male and female patients with FAT (Fig. 37.1) [2,13].

The three mechanisms of FAT are as follows: reentry, automaticity, and triggered activity. Reentry and triggered activity are challenging to differentiate using electropharmacological studies [14]. Hu et al. suggested that men with FAT had a higher incidence of increased automaticity as the mechanism, which is defined as tachycardia that could not be initiated or terminated by programmed electrical stimulation [2]. Similarly, Kammeraad et al. reported that patients with nonautomatic FAT diagnosed using the same criteria were predominantly female (n = 31, 82%), with the mean age at presentation of 31 years [15]. Structural heart disease or prior heart surgery was not found in these patients [15]. Both studies suggested that the mechanism of automaticity may be linked to the male sex; however, these studies did not explore the FAT mechanisms of reentrant circuits and triggered activity. In previous studies, the adenosine test was applied to patients with FAT to differentiate between triggered activity and reentrant circuits (n = 76) [16,17]. All patients with adenosine-insensitive FAT (n = 6; 100%), suggested to be caused by reentrant circuits, were male and had significant

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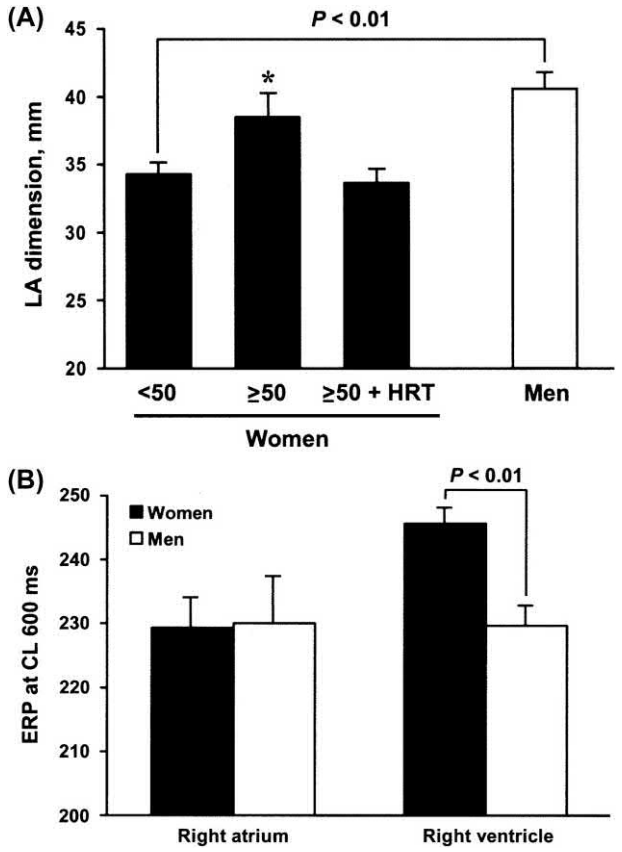

FIGURE 37.1 Sex differences of left atrial dimension and effective refractory period. (A) Comparison of left atrial (LA) dimension among 29 women <50 years old, 10 women ≥50 years old, and 7 women ≥50 years old receiving hormone replacement therapy (HRT) and between the women and 22 men. *$P < .05$ compared with women <50 years old and with women ≥50 years old and receiving hormone replacement therapy. (B) Right atrial and right ventricular effective refractory period (ERP) at a cycle length of 600 ms in 39 men and 76 women [13]. Error bars, SEM. *Reprinted with permission from Elsevier.*

comorbidities or cardiac disease (Fig. 37.2) [17]. However, only 50% (35/70) of patients with adenosine-sensitive FAT (mostly caused by triggered activity according to the authors' criteria) were male [17]. Overall, the data suggest that the mechanism of FAT in men, rather than in women, might be automaticity or reentrant circuits. Table 37.1 summarizes the clinical and electrophysiological characteristics of male and female patients with FAT.

Underlying mechanisms of focal atrial tachycardia

Tissue or cellular electrophysiology

Tissue and cellular electrophysiology in atrial cardiomyocytes differ between women and men. Compared with female rabbits, male rabbits had more delayed afterdepolarizations in their left atrium (LA) and pulmonary vein, but not in the right atrium (RA), in perfused isolated atrial tissue [18]. The LA of male rabbits had longer action potential durations (APDs) than that of female rabbits. Isoproterenol administration shortened APDs in female rabbits but not in male rabbits. Acetylcholine administration shortened APDs in both female and male rabbits without any differences [18]. Similar phenomena were observed in isolated cardiomyocytes from the LA posterior wall in male rabbits, which exhibited more delayed afterdepolarizations than female rabbits (Fig. 37.3) [19]. A cardiac glycoside, which inhibited Na^+/K^+-ATPase and increased Na^+ and Ca^{2+} accumulation, induced more trigger activities in male animals than in female animals. No difference was observed in the trigger activities of isolated cardiomyocytes from the RA between male and female animals. The increased late sodium current, calcium transients, and sarcoplasmic reticulum calcium storage were identified as the underlying mechanisms [19]. In male patients, FAT is more commonly identified in the LA than in the RA. These data evidence the underlying sex differences in FAT in the LA, but not in the RA. Although differential atrial electrophysiological studies in experimental models indicated sex differences, atrial electrophysiological characteristics did not differ between men and women in human studies [20,21]. No significant sex differences were observed in the refractory periods in the right and left atria, endocardial bipolar voltage, and pulmonary vein and atrial conduction time in patients with AF or SVT [13,21].

Structural diversity

Men have a significantly larger average LA dimension and volume than women [13,22]. When the sex difference in the body surface area was considered, the LA volume index (left atrial volume/body surface area) did not differ between men and women, but the right atrial volume index was higher in male athletes [22]. No difference was found in atrial dilatation (left atrial volume index >34 mL/m^2) between male and female athletes. The altered left atrial structural remodeling promoted reentry and triggered activity mechanisms. In the same study, Wilhem et al. also noted different hemodynamic status, that is, higher blood pressure in male athletes than in female athletes [22]. Because men with FAT usually have more cardiovascular comorbidities, differential atrial remodeling between women and men may be secondary to systemic and cardiovascular diseases. Atrial remodeling secondary to age and comorbidities may increase the development of FAT resulting from triggered activity or reentry, leading to sex differences [4,11]. Moreover, several hypotheses support that intrinsic structural changes play a role in sex differences in FAT. The myosin heavy chain β-isoform (MHC-β, slow twitch) is expressed primarily in the heart and is associated with heart failure. Compared with men, women

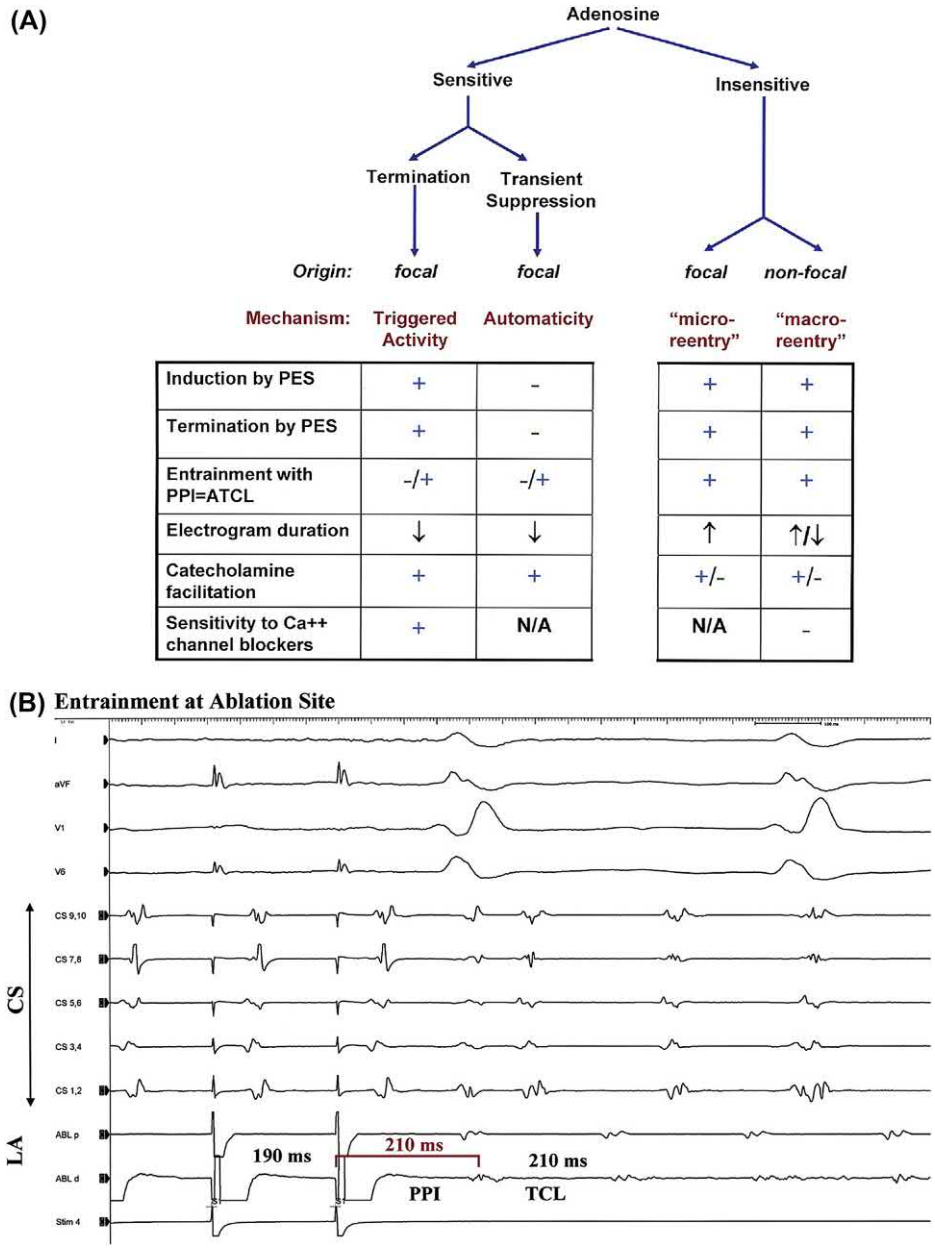

FIGURE 37.2 **The mechanisms of focal atrial tachycardias.** (A) Adenosine-sensitive focal atrial tachycardia (FAT) is mostly due to triggered activity or, far less commonly, automaticity. Adenosine-insensitive FAT is either macroreentrant or microreentrant, depending on circuit size and the resolution of the mapping system. (B) The postpacing interval after the entrainment approximates the tachycardia cycle length, suggesting of the reentrant mechanism [17]. *Reprinted with permission from Elsevier.*

without heart failure showed a twofold higher amount of MHC-β in the LA. A slightly higher amount of MHC-β in the RA was found in women. The MHC-β amount in LA and RA did not differ between men and women in the patients with congestive heart failure. The sex differences in the MHC isoform amount may be attributed to altered atrial functional and structural remodeling, especially to the remodeling during physiologically stressful events [23]. Amyloidosis deposition may differ between women and men, potentially leading to inflammation, loss of cardiomyocytes, and atrial fibrosis [24]. Amyloidosis deposition is more common in female patients with chronic AF

TABLE 37.1 **Gender differences in clinical and electrophysiological characteristics for focal atrial tachycardia.**

	Male	Female
FAT incidence		+
Right atrial focus		+
Second tachycardia		+
Comorbidities	+	

Continued

TABLE 37.1 Gender differences in clinical and electrophysiological characteristics for focal atrial tachycardia.—cont'd

	Male	Female
The number of FAT foci	+/−	+/−
Tachycardia cycle length	+/−	+/−
Right atrial effective refractory period	+/−	+/−
Right atrial functional refractory period	+/−	+/−
Reentry/automaticity	+	
Left atrial size	+	
Right atrial size	+	
Right atrial voltage	+/−	+/−
Left atrial voltage	+/−	+/−
Sympathetic tone (LF/HF, heart rate variability)	+	
Cyclic change of arrhythmic episodes		+
Proarrhythmias after antiarrhythmic medications		+
Ablation outcome	+/−	+/−

+/−, no difference between men and women; +, significantly higher; *FAT*, focal atrial tachycardia; *LF/HF*, low frequency/high frequency.

and rheumatic heart diseases and is correlated with AF duration [24]. However, how these pathological changes interact with structural remodeling of atria remains to be elucidated.

Autonomic tone

In an analysis of heart rate variability, male athletes had a higher power ratio of the low-frequency (LF)/high-frequency (HF) band during the day and night than female athletes [22]. Similar findings were also demonstrated in healthy subjects (Fig. 37.4) [22,25,26]. These findings suggest that men have a higher sympathetic tone than women. In addition to central autonomic regulation, the expression and regulatory mechanisms of cardiac autonomic receptors may be different in women and men. The total amount of β-adrenoceptors in the isolated LA was higher in male rats than in female rats, which correlated with the gradient of cAMP [27]. Cardiac β-adrenoceptor overexpression leads to progression to the cardiomyopathic phenotype, which is exacerbated by testicular hormones (especially 5α-dihydrotestosterone) [27,28]. Depletion of ovarian hormones through oophorectomy also increased the expression of β-adrenoceptors, indicating the competitive roles of sex hormones in the autonomic regulation of cardiomyocytes [27].

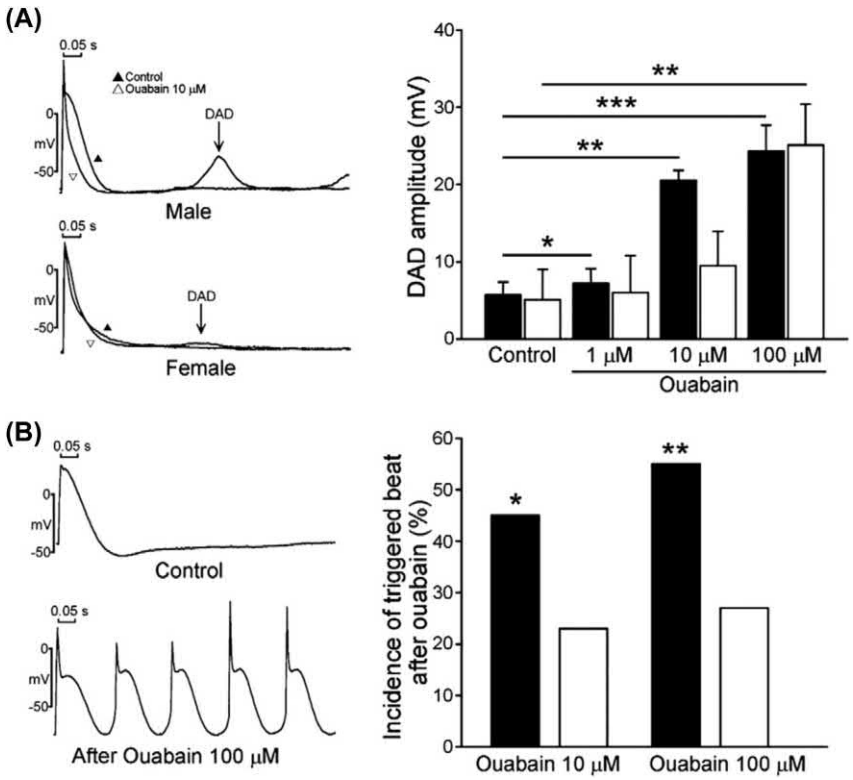

FIGURE 37.3 Sex differences of triggered activity in atrial cardiomyocytes. (A) Representative action potential recording after the treatment of ouabain (10 μM, left panel). The amplitude of delayed afterdepolarizations (DADs) was higher in male than female myocytes. There was a higher amplitude of DADs in male than female left atrial myocytes after ouabain treatment (right panel). Average data show the changes of DAD amplitude after ouabain perfusion (1, 10 and 100 μM) in male (n = 13) and female (n = 13) myocytes. (B) Representative recording of ouabain (100 μM)-induced triggered beats in male left atrial wall myocytes. The bar graph shows the incidence of ouabain-induced triggered beat in male and female myocytes [19]. Male: black bar, female: white bar. *$P < .05$; **$P < .01$; ***$P < .005$ versus control myocytes. *Reprinted with permission from Elsevier.*

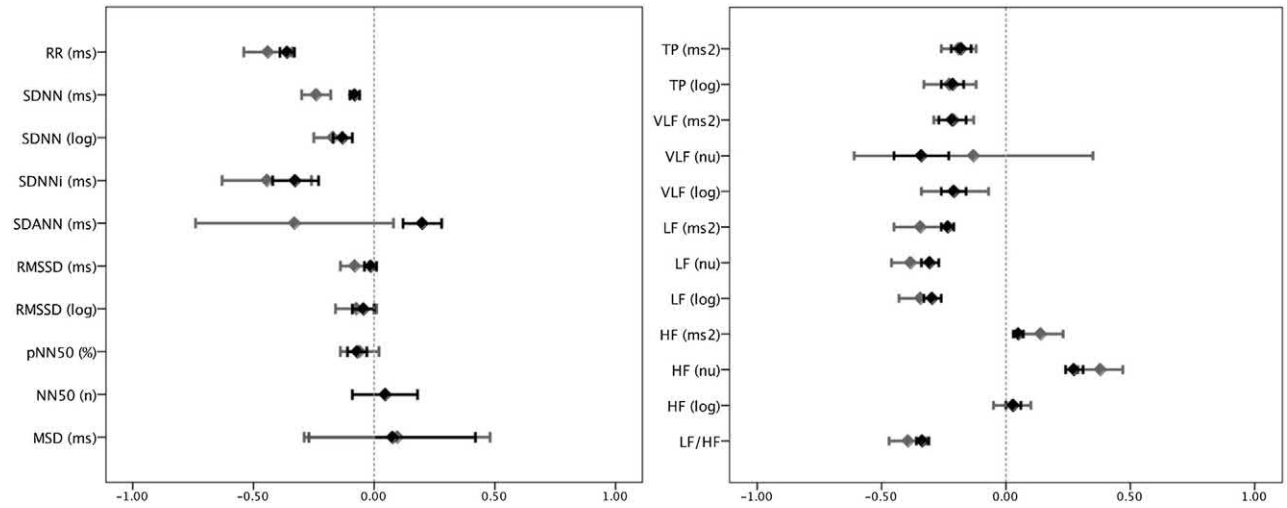

FIGURE 37.4 **Sex differences on heart rate variability measures.** Meta-analysis on sex differences on heart rate variability measures. Black: fix-effect models; gray: random-effect models; a positive effect size indicates that the respective measure is greater in women compared to men. The ratio of LF to HF power (LF/HF ratio) estimates the ratio between sympathetic nervous system and parasympathetic nervous system activity. Male has higher sympathetic activity than female does [26]. *Reprinted with permission from Elsevier.*

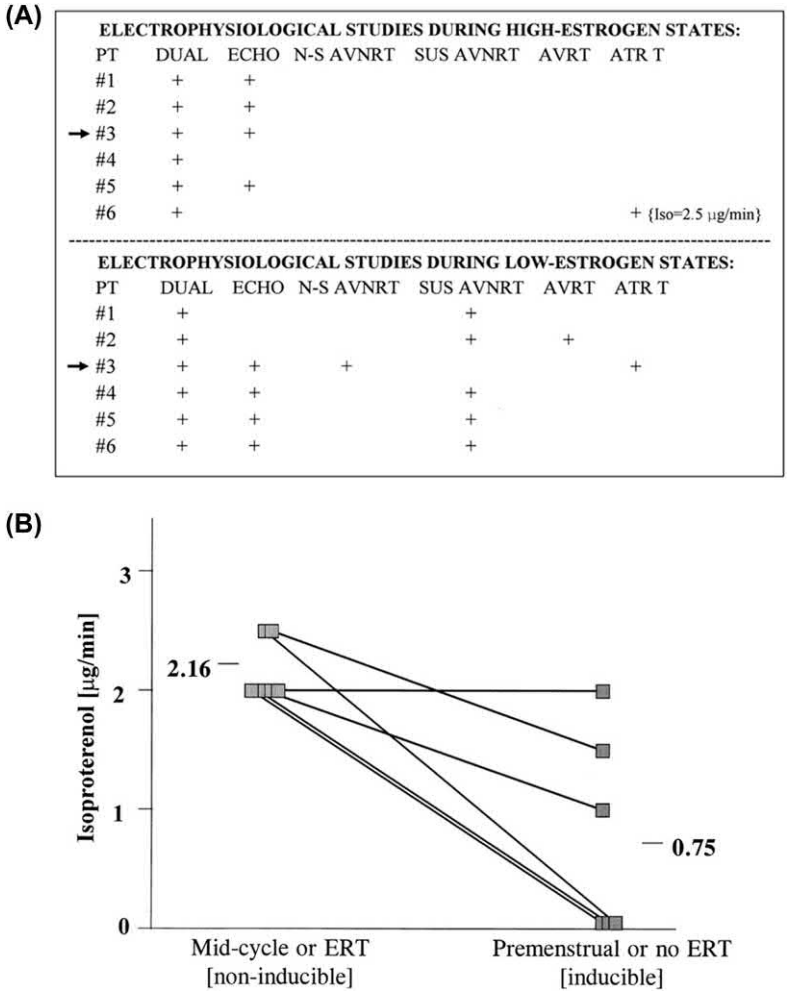

FIGURE 37.5 **Inducibility of focal atrial tachycardia according to estrogen states.** (A) Results of paired electrophysiologic studies during high estrogen states (midcycle or estrogen therapy) and low estrogen states (perimenstrual, estrogen withdrawal) among women with perimenstrual clustering of supraventricular tachycardia (SVT). During the high estrogen state studies, four of six patients demonstrated echo beats (ECHO), but none had nonsustained (N−S) or sustained (SUS) atrioventricular nodal tachycardia (AVNRT) or other sustained SVTs. One patient had nonsustained atrial tachycardia (ATR T) induced during isoproterenol (Iso) infusion. During low estrogen states, five of the six patients had sustained AVNRT induced. One of them had AV reentrant tachycardias. In one other patient, nonsustained AVNRT and a sustained ectopic atrial tachycardia (during isoproterenol infusion) were induced. DUAL: dual AV nodal pathway physiology. (B) Isoproterenol infusion and inducibility. Among six patients whose tachycardias were noninducible with isoproterenol infusions during high estrogen state (the initial study). During the repeat studies (low estrogen state), three of the six patients required no isoproterenol for induction of sustained arrhythmias. The peak dose was based on the infusion rate required to achieve a >30% increase in sinus rate during steady-state infusion [30]. *Reprinted with permission from Elsevier.*

Sex hormones

It remains unclear whether menstruation affects FAT episodes or durations. The episodes and durations of AVNRT or atrioventricular reentry tachycardia (AVRT) were positively correlated with the plasma levels of progesterone but negatively correlated with 17-estradiol levels [29]. Women with cyclical patterns of spontaneous tachycardia tended to have negative electrophysiologic study results at midcycle or when receiving estrogen replacement therapy (Fig. 37.5) [30]. Compared with postmenopausal women, premenopausal women had a higher incidence of the FAT mechanism of increased automaticity (13.4% vs. 2.9%) [2]. Associated arrhythmia, FAT number, left atrial involvement, nonparoxysmal tachycardia, and shortest cycle exhibited no difference between women with or without menopause. The administration of 17-β estradiol changed atrial ERP in dogs (Fig. 37.6) [31]. The antiarrhythmic effect of ovarian hormones was not found in cell and animal studies. In addition to the suppression of β-adrenoceptors [27], estrogen regulates ion currents in atrial cardiomyocytes [32]. In single guinea pig atrial myocytes, 17b-estradiol shortened the APD but did not change the resting membrane potential [32]. In the myocytes, 10 μM of 17b-estradiol reduced $I_{Ca.L}$ but did not change I_{CaT}, I_{Kr}, I_{Ks}, and inwardly rectifying K^+ current [32]. The estrogen concentrations (ranging from 3 to 10 μM) in this cellular study were higher than the physiological concentration of estrogen (less than 1 μM) [33]. Therefore, the clinical relevance if the study findings should be further validated. Table 37.2 summarizes the experimental electrophysiological and molecular characteristics of men and women.

TABLE 37.2 Gender differences in experimental electrophysiological and molecular characteristics in the atrium.

	Male	Female
Left atrial action potential duration	+	
Left atrial delayed afterdepolarization	+	
Right atrial action potential duration	+/−	+/−
Right atrial delayed afterdepolarization	+/−	+/−
Late Na^+ current	+	
L-type Ca^{2+} current	+	
β receptors	+	
Myosin heavy chain isoform ß		+
Amyloid deposition		+

+/−, no difference between women and men; +, significantly higher.

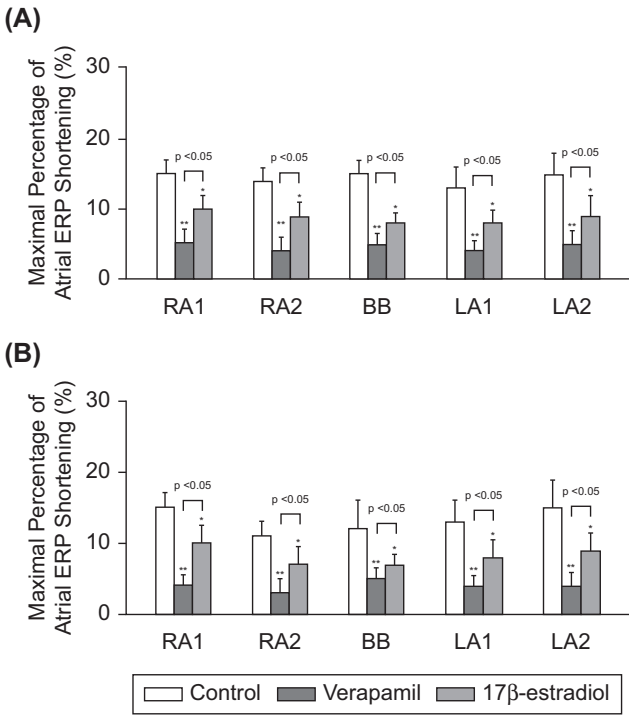

FIGURE 37.6 The changes of atrial effective refractory period after the treatment of estrogen. Maximal changes of atrial effective refractory periods (ERPs) shortening at the pacing cycle length of 350 ms (panel A), and 250 ms (panel B). The ERP from five epicardial atrial sites were measured before and after rapid atrial pacing at 800 beats/min for 30 min in dogs with the pretreatment of verapamil (n = 10), 17β-estradiol (n = 10), or without the pretreatment (n = 10, control group). The maximal changes of atrial ERP shortening at both pacing cycle after the treatment of 17β-estradiol (0.3 μg/kg for loading and 0.02 μg/kg per hour for the maintenance) was shorter than those without any treatment [31]. *Reprinted with permission from John Wiley and Sons.*

Therapeutic implications

Intrinsic sex differences in cardiac tissue resulting from variable ion channel expression, sex hormones, and autonomic regulation may cause differences in drug responses. The female sex is a risk factor for drug-induced cardiac arrhythmia, especially torsade de pointes [34]. Because antiarrhythmic drugs exert detrimental proarrhythmic effects, the use of these drugs must be carefully monitored in women; occasionally, dose reduction or discontinuation might be conducted, if required [35]. Based on the aforementioned clinical and experimental evidence, it is expected that differential antiarrhythmic effects of antiarrhythmic drugs exist in women and men; however, clinical data are lacking. Catheter ablation is considered front-line therapy for FAT. To schedule elective electrophysiologic procedures might facilitate arrhythmia induction when estrogen levels are low (premenstrual status or estrogen replacement therapy discontinuation) in women with a history of perimenstrual clustering of arrhythmic

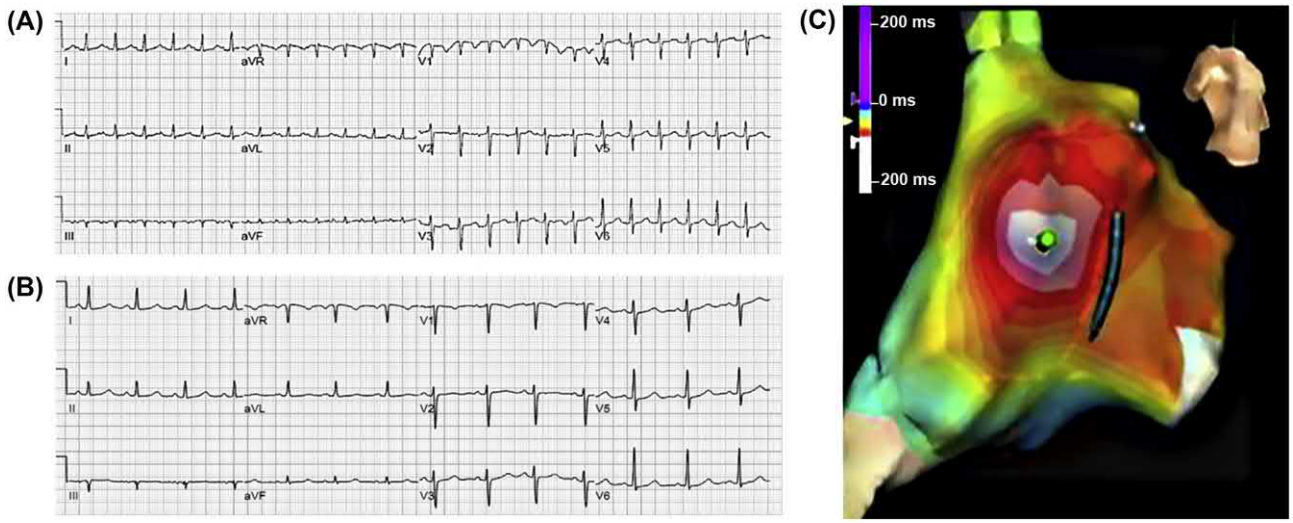

FIGURE 37.7 Radiofrequency catheter ablation of incessant atrial tachycardia in a pregnant woman with minimal radiation exposure. (A) 12-Lead electrocardiogram (ECG) from the patient showing atrial tachycardia originating from the high crista terminalis. (B) ECG after successful focal atrial tachycardia ablation. (C) 3D electroanatomical map showing a centrifugal pattern of activation originating from the right atrial free wall [40]. *Reprinted with permission from Elsevier.*

episodes and among those receiving estrogen replacement therapy. Outcomes after catheter ablation include immediate success, FAT recurrence, and complications, which generally did not significantly differ between women and men [1,2]. No difference was found in the success and recurrence rates after catheter ablation in women with or without menopause and premenopausal women [2].

Pregnancy

FAT is one of most prevalent causes of arrhythmia in pregnant women [36]. Arrhythmia management during pregnancy should consider various clinical factors, including the presence of the fetus, the risk of teratogenicity, hemodynamic changes, and the effect of therapy on labor, delivery, and lactation [37]. Several antiarrhythmic agents, such as propranolol, metoprolol, digoxin, and quinidine, have been extensively tested during pregnancy [37]. These drugs are probably safe, but it is still suggested that they should be avoided in the first trimester. Intravenous adenosine may be used to treat arrhythmia caused by reentrant circuits [38]. However, compared with other supraventricular tachycardias such as AVRT or AVNRT, patients with FAT usually show poor responses to these medications. Successful catheter ablation of drug-refractory FAT in pregnant women under the guidance of a three-dimensional electroanatomical map has been reported, with minimal radiation exposure (Fig. 37.7)[34,37–39]. Although most procedures have favorable outcomes without the incidence of any complications, the risk of complications is still high [36,39–41]. For example, one patient experienced a pulmonary embolism immediately after the procedure and miscarried [40]. Ablation is only suggested in pregnant women with poorly tolerated drug-refractory FAT, preferably during the second trimester [42].

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Chapter 38

Accessory pathway and atrioventricular reentrant tachycardia

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Approximately half of all paroxysmal supraventricular arrhythmias are atrioventricular nodal reentrant tachycardia (AVNRT), more common in women than in men. The circuit usually contains two anatomical pathways, one fast and one slow. Both are placed in the right atrium. The tissue of these pathways has similar conduction properties as the atrioventricular node and is often perceived as a part of the atrioventricular node. AVNRT usually occurs before 40 years of age. This particular arrhythmia is described in detail in a different chapter of this book [1].

The second most common mechanism of paroxysmal supraventricular tachycardia (SVT) is atrioventricular reentrant tachycardia (AVRT). It is based on the presence of an accessory pathway, and it is associated with Wolff−Parkinson−White syndrome (WPW syndrome). Accessory pathway tachycardias and asymptomatic preexcitation are more common in men, while atrioventricular nodal reentry tachycardia and focal atrial tachycardia are more seen in women.

Electrophysiological properties of the accessory pathway are similar to working myocardium. Accessory pathway conducts more rapidly than the normal atrioventricular node, but it is characterized by a longer recovery time. Orthodromic type of reentry circuit is observed more often. A premature atrial beat is not able to penetrate the accessory pathway because of refracterity. The impulse heads to the ventricle through the normal atrioventricular node, whose conductivity has decremental properties. Conductivity of the accessory pathway is restored in the meantime. The impulse returns to the atrium retrogradely through the accessory pathway, and a continuous conduction circuit of tachycardia is closed. Accessory pathways may conduct electrical stimulus anterogradely, retrogradely, or bidirectionally. Only retrograde accessory pathway conduction does not affect the baseline ECG, and the delta wave is not visible. These pathways are called concealed. Tachycardia resulting from this mechanism can be suspected on surface electrocardiogram, when the QRS complex is normal and the retrograde P wave occurs after the QRS complex, in the ST segment or early in the T wave (Fig. 38.1). Minority of patients are characterized by antidromic type of conduction. The activation wave continues to the ventricle over the accessory pathway and returns to the atrium retrogradely through the atrioventricular node. These accessory pathways are called manifest. In this case, ECG is characterized by short PQ interval less than 120 ms during sinus rhythm, QRS duration exceeding 120 ms with a slow rising onset (delta wave) in some leads and secondary ST-T wave changes. The most common antidromic tachycardia is characterized by an abnormal QRS, a regular rhythm, and ventricular rate about 150−250 beats per minute, usually faster than in atrioventricular reentry tachycardia [2] (Figs. 38.2−38.4).

Concealed accessory pathways are more frequently localized in the left side (93% left, 7% right). Manifest accessory pathways are seen in the left side in about two-thirds of the cases (64% left, 29% right) and in 7% in the posteroseptal left and right region. There is no sex difference observed. Tachyarrhythmia because of concealed accessory pathway is usually seen in older age than the manifest accessory pathway arrhythmia. These patients also often present with a longer history of tachycardia [3]. By definition, the WPW syndrome requires evidence of preexcitation in the ECG and a presence of paroxysmal tachycardia. The prevalence in western countries is of 1.5−3.1 per 1000 persons [4]. It is not clear whether there is an underlying genetic cause to the WPW syndrome. In the majority of cases, the WPW syndrome has no straightforward familiar dependency. In some patients, the WPW syndrome is a part of a complex genetically based syndrome, or it results from an inherited condition [5]. The tachycardia can also circulate between two

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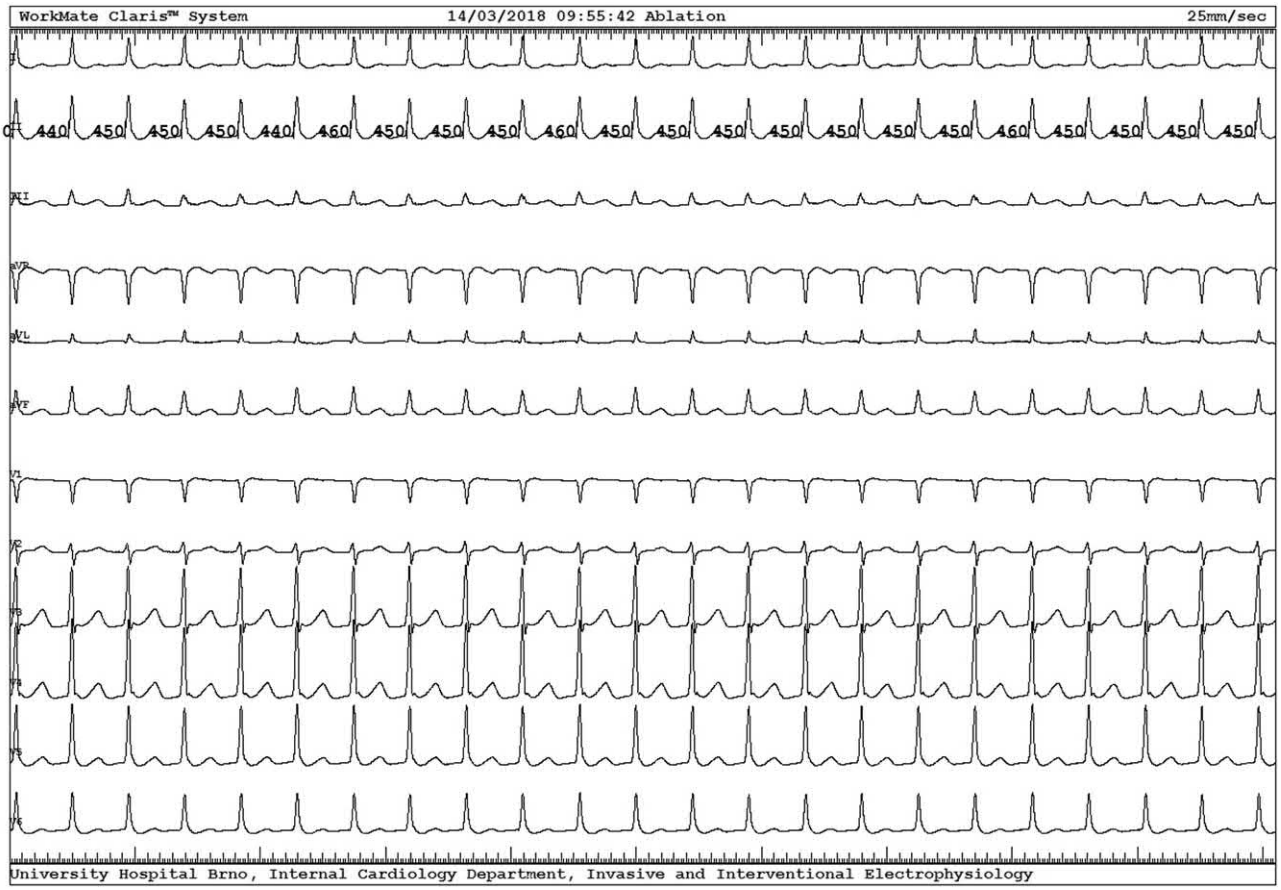

FIGURE 38.1 **Orthodromic type of atrioventricular reentrant tachycardia (AVRT).** In this type of AVRT, delta wave is not present, the QRS complex is normal, and retrograde P wave occurs after the QRS complex.

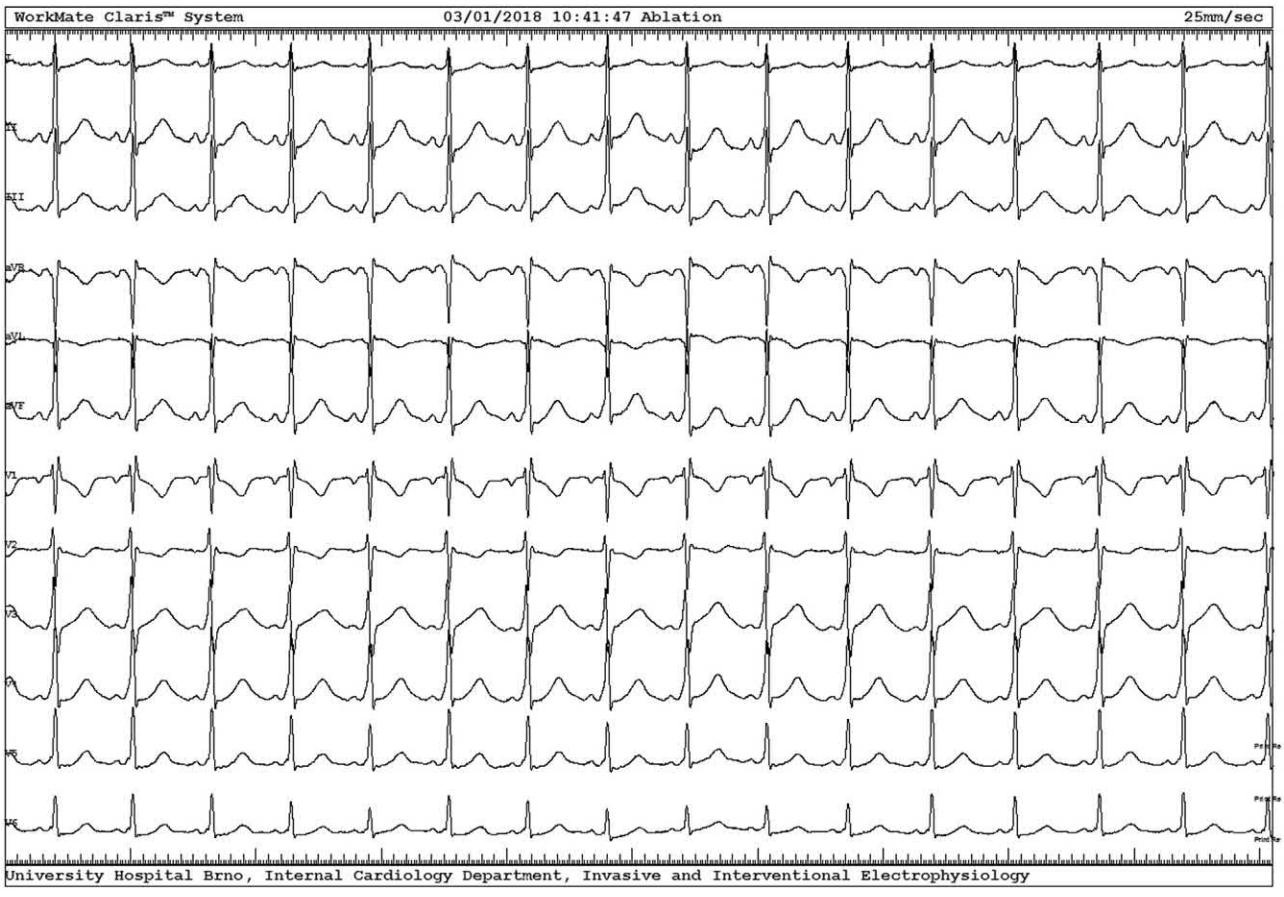

FIGURE 38.2 **Antidromic type of atrioventricular reentrant tachycardia.** This ECG shows preexcitation of right bundle branch block morphology—left-sided accessory pathway.

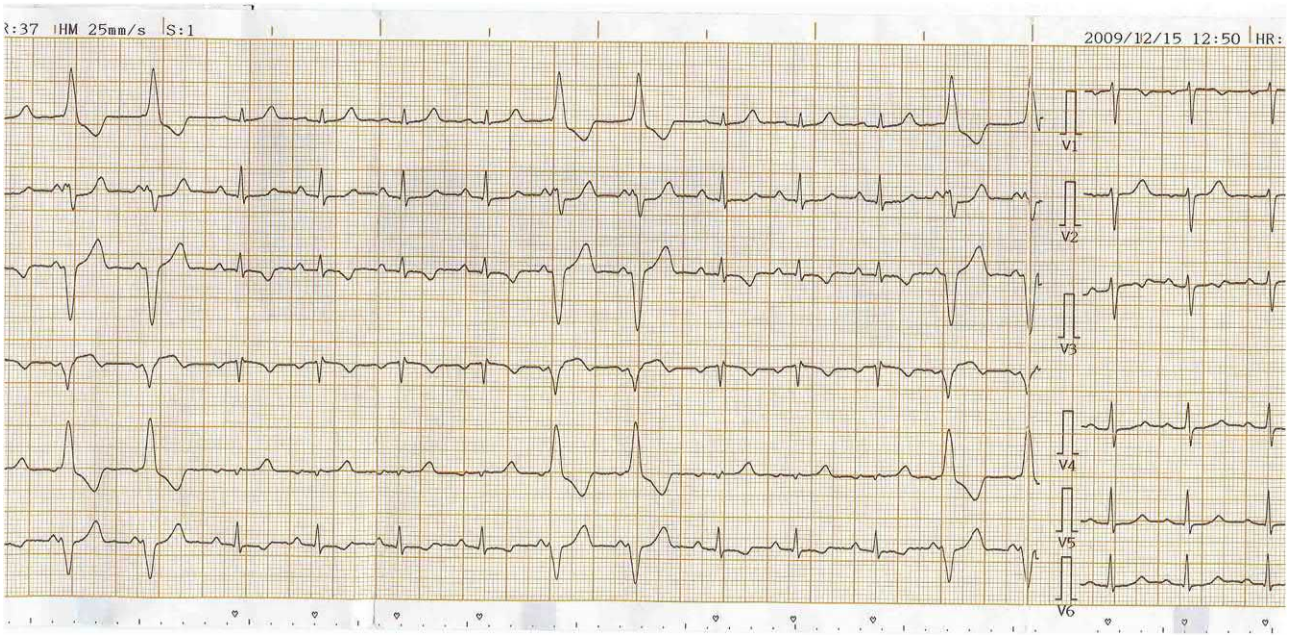

FIGURE 38.3 **Intermittent preexcitation of left bundle branch block morphology—right-sided accessory pathway.** This example enables a comparison of preexcited and non-preexcited QRS complexes in tracing ECG.

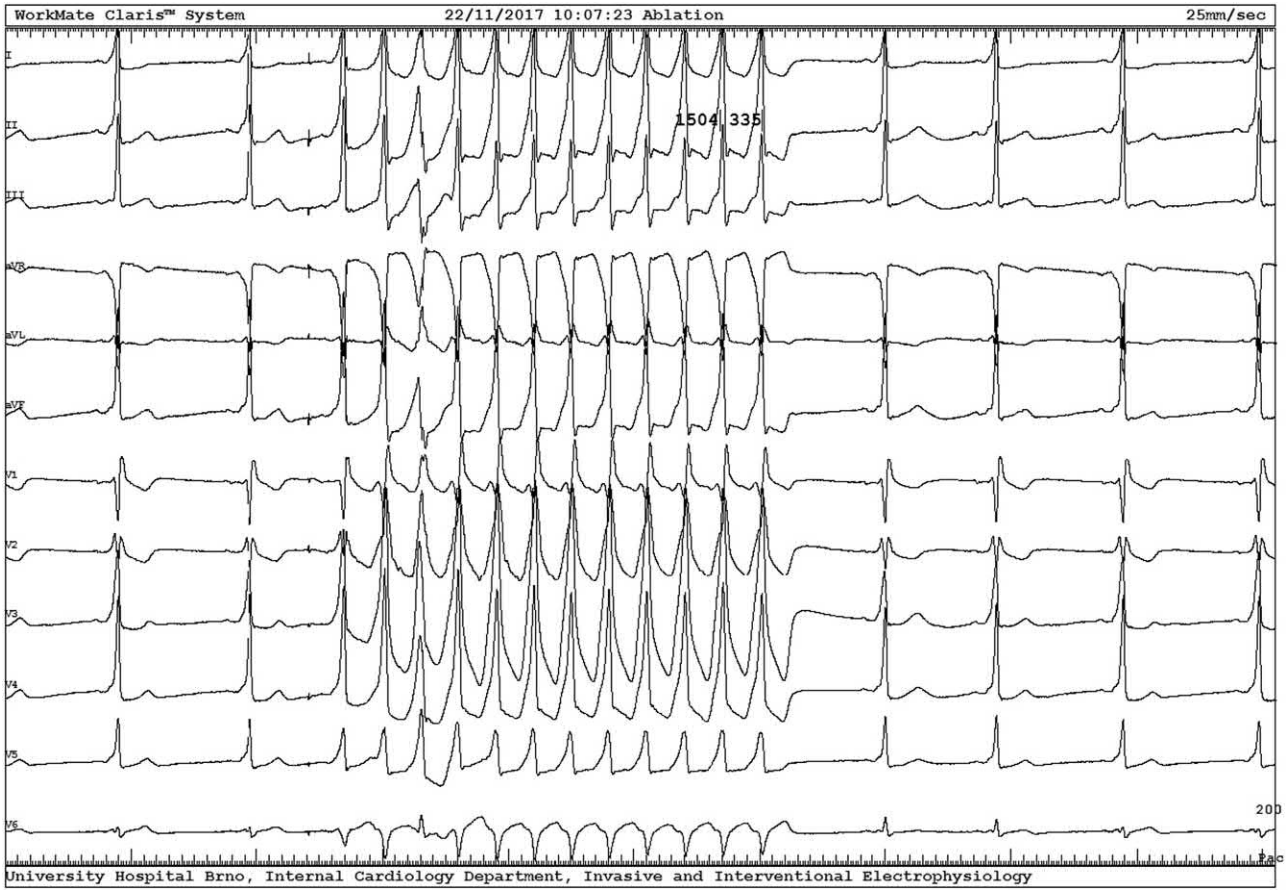

FIGURE 38.4 **Antidromic type of atrioventricular reentrant tachycardia.** This ECG shows short PQ interval and manifests delta wave on the onset of QRS. In the central part of this picture, a paroxysmal, spontaneously terminating tachycardia is recorded.

accessory pathways, omitting atrioventricular node. Some of these pathways do not directly connect atrium and ventricle; the connection may be nodofascicular or nodoventricular. The impulse runs anterogradely through the accessory pathway, and it uses the His-Purkinje fibers and a portion of the atrioventricular node as the retrograde conduction way. The Lown–Ganong–Levine syndrome (short PR interval and normal QRS complex) features a pathological conduction way in the form of the James fiber, which connects the atrium to the distal portion of the atrioventricular node. His bundle closes the circuit by leading the impulse back. All these atypical accessory pathways may have similar electrophysiological properties as the atrioventricular node [6].

As can be seen in pediatric patients, the mechanism of SVT and sex differences may vary during life. With increasing age, the frequency of accessory pathway tachycardias decreases. On the contrary, the rate of the AVNRT increases. Some studies show that the sex differences between these two types of arrhythmia are age-dependent. In the 12–21 years age group, women are more likely to have an AVNRT than an accessory pathway. No significant sex differences were found at the younger ages. This could be explained by the influence of the sex hormones in adolescence [7]. Tachycardia diagnosed in infancy can disappear in adulthood. The pathway can lose its ability to conduct anterogradely [2].

Coincidence with paroxysmal atrial fibrillation in AVRT patients presents a potentially life-threatening condition. The very fast atrial fibrillation tachycardia can, in some cases, send the stimulus through the accessory pathway. This accessory pathway conduction is very rapid and without decrement in contrast to decremental conduction over atrioventricular node with the possibility of blockade protection. This may lead to ventricular fibrillation and sudden cardiac death. This very serious complication is more frequently observed in older patients and in patients with manifest accessory pathway with anterograde conduction. Generally, this does not seem to be sex-dependent. However, some studies show that anterograde accessory pathway with an effective refractory period shorter than 250 ms, which is suggested to associate with higher risk for sudden cardiac death, was more common in men [8]. On the opposite, accessory pathways are suspected to play an independent role in the pathogenesis of atrial fibrillation in patients with WPW syndrome [9] (Figs. 38.5 and 38.6).

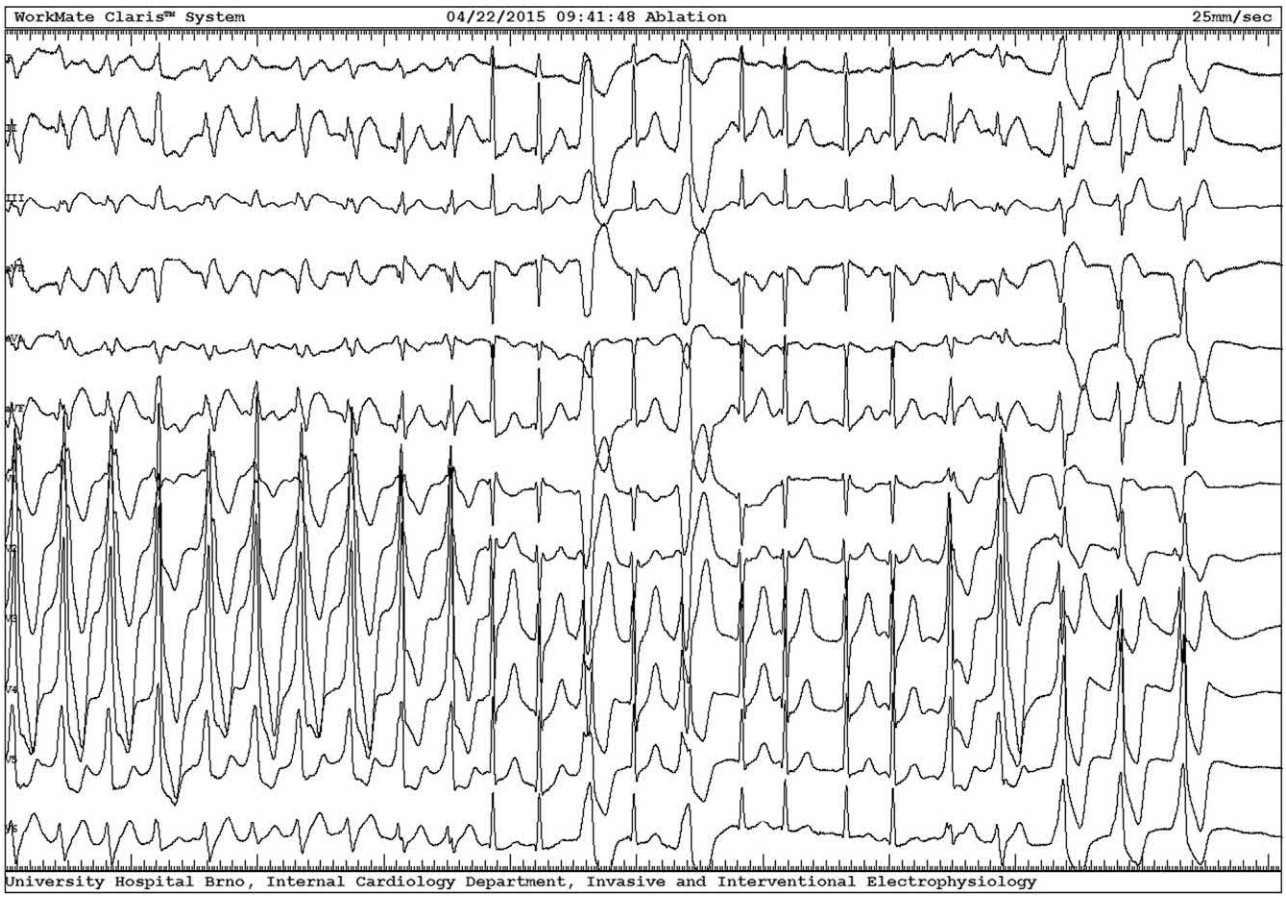

FIGURE 38.5 **Atrial fibrillation and accessory pathway.** This ECG shows atrial fibrillation progradely conducted through the accessory pathway.

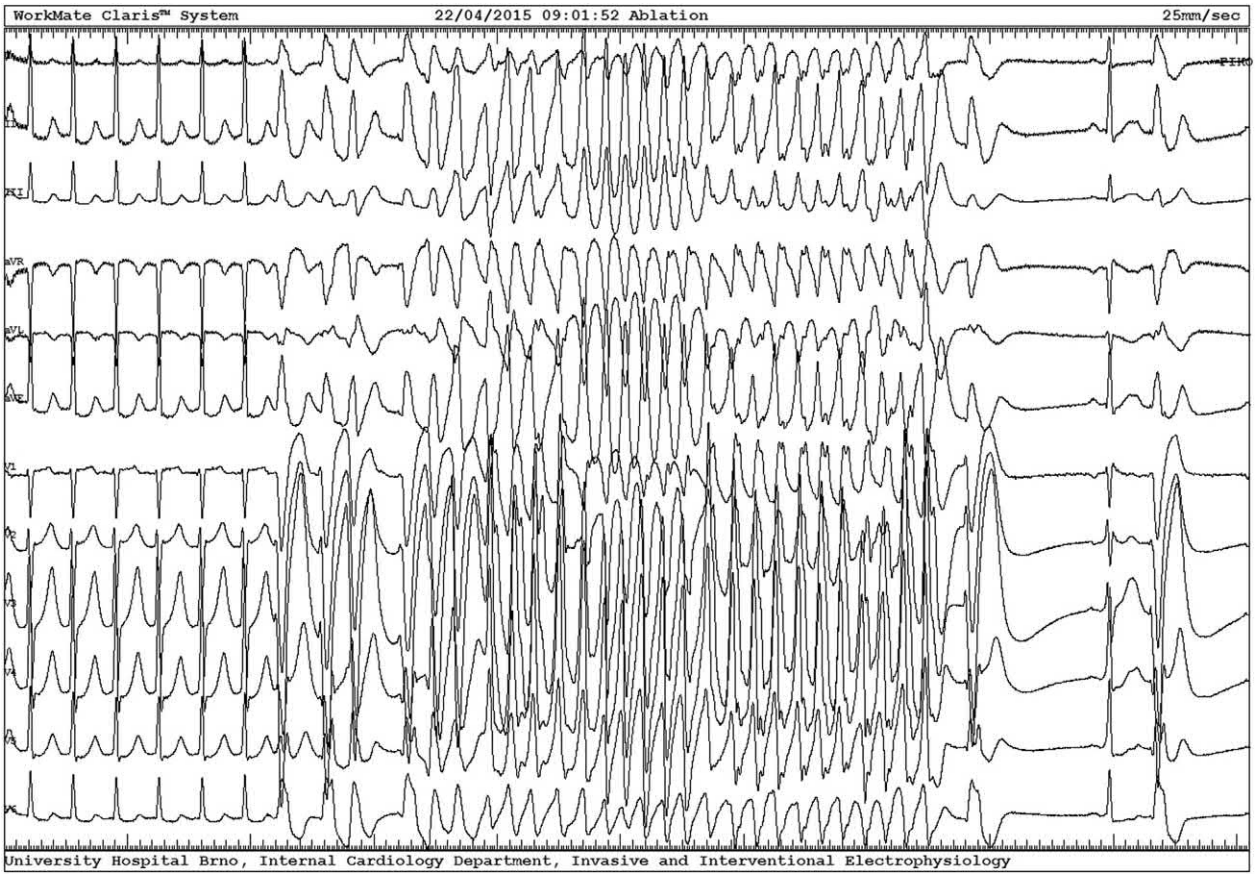

FIGURE 38.6 **Atrial fibrillation and accessory pathway.** This ECG shows atrial fibrillation conducted through the accessory pathway, resulting in fast ventricular tachycardia.

There are some differences between men and women in the normal electrophysiology of the conduction system and working myocardium. Hormones, drugs, and electrolytes affect cardiac ion channels differently in men and women, and this results in sex-specific conduction properties. The explanation may also be the different cardiac size and myocardium structure in both sexes [10]. These sex differences are the electrophysiological substrate for the reason why the AVNRT is more common in women and the accessory pathways are more frequent in men. Men have a longer atrial effective refractory period than women, but shorter ventricular effective refractory period. Women have an enhanced atrioventricular node function, as can be seen in shorter PR and AH interval detection. This, in combination with a shorter atrioventricular node effective refractory period and shorter Wenckebach cycle length, makes women more prone to develop an AVNRT. On the other hand, shorter anterograde accessory pathway effective refractory period, higher prevalence of an anterograde conducting accessory pathway, and a longer atrioventricular nodal effective refractory period are consistent with higher occurrence of accessory pathway-based arrhythmias in men. Women statistically show not only more concealed and fewer manifest but also more multiple accessory pathways. The tachycardia window, defined as the difference between the anterograde atrioventricular nodal effective refractory period and the accessory pathway effective refractory period, is the same for men and women [8] (Fig. 38.7).

Observations of cohorts of patients have demonstrated that there is no significant difference in baseline heart rate, tachycardia cycle length, and catecholamine-responsive rate during orthodromic and antidromic AVRT between men and women. Autonomic regulation probably does not play the main role in explaining the shorter anterograde accessory pathway effective refractory period in men [11]. Sex hormones seem to be more influential in that regard. Estrogen is assumed to regulate myocyte metabolism, influence myocyte regeneration and cytoprotection, stabilize the electrophysiological functions, and contractile ability of myocytes. It may also change the atrial effective action potential and atrioventricular nodal conduction. Testosterone and progesterone shorten, whereas estrogen prolongs the QT interval. The underlying mechanism is still not satisfactorily described, but it is thought to be linked to body temperature and an increased sympathetic activity

	MEN	WOMEN
ATRIAL ERP	Longer	Shorter
VENTRICULAR ERP	Shorter	Longer
ATRIO – VENTRICULAR CONDUCTION	Slower	Faster
WENCKEBACH CYCLE LENGHT	Longer	Shorter
ANTEROGRADE AP ERP	Shorter	Longer
ACCESSORY PATHWAY	More common	More concealed

FIGURE 38.7 Sex differences in selected electrophysiologic parameters. Comparison of selected conduction properties in men and women. *ERP*, effective refractory period.

[12–14]. Tachycardia episode rates vary according to the phases of the menstrual cycle. The luteal ovarian phase is characterized by such progesterone and estrogen level fluctuations, which make women at this time more prone to tachycardia episodes. Electrophysiologic examination and invasive therapeutic procedures performed at the time of low estrogen level (premenstrual) should lead to more successful results because of easier inducibility of SVT [15–17].

As stated above, pregnancy presents an exceptional hormonal state. Some studies detected increased incidence of new onset and also more frequent exacerbations of preexisting SVTs during pregnancy. Strong hormonal and hemodynamic changes, changes in autonomic tone, and higher myocardial cells irritability are probably the culprits. Increased expression of the α-adrenergic receptors makes the myocard more sensitive to catecholamines [18].

Concerning the localization of the accessory pathways in general, the left free wall accessory pathways are the most common, followed in frequency by posteroseptal, right free wall, and anteroseptal locations. Three major studies contained sex variability data of different accessory pathway locations. They show conflicting results. The Israeli study included 804 patients, 511 males (63.6%) and 293 (36.4%) females, mean age 34 + 16 years, who underwent their first RFA of a single accessory pathway. The accessory pathway was located mostly in the left free wall (57.8%), posteroseptal (22.8%), right free wall (9.3%), right anteroseptal (7%), and other locations (3.1%). Men and women had similar frequency of the left free wall accessory pathway (58.1% and 57.3%) and the same result was in posteroseptal location, where there was also no significant sex difference (23.1% and 22.2%). The right free wall location was more frequent in females (13%) than in males (7.2%). The right anteroseptal location was more frequent in males (8.4%) than in females (4.4%). These findings were significant in the subgroup of Jewish patients in this study. Among the non-Jewish patients, there was no statistical correlation between the accessory pathway location and the sex. This fact may result from the small number of patients in this subgroup, but ethnical and racial differences are to be better understood [19]. The Israeli study findings are in accordance with the results of the study by Hsu et al. who compared race and sex with accessory pathway location in 282 American patients from the San Francisco area. They found that 57% of females had right annular accessory pathway compared with 32% of men. Men had more frequent left posterior location of accessory pathway (52% and 36%). This study concluded that patients of Asian origin presented with 3.8-fold more frequent right anterior accessory pathway compared with other races, which hints back at the idea of racial differences [20]. In contrast, results from retrospective observation study including 942 patients in hospital Sao Paulo in Brazil bring different findings, which are inconsistent with previously described two studies. This study detects statistically significant sex differences in accessory pathways located in left posterior and right lateral segment with a predominance of the male sex [21]. Further studies are probably needed to coordinate research in the field of sex and accessory pathway location correlation.

The age of AVRT onset seems to be higher in men than in women (39.4 ± 18.0 years vs. 34.4 ± 16.5 years) (Fig. 38.8). The peak incidence of the arrhythmia suitable

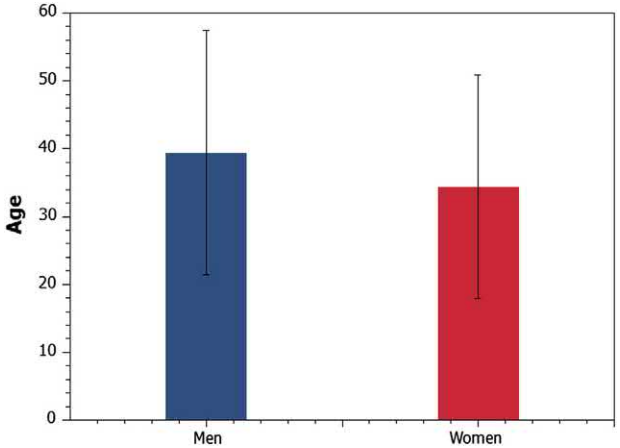

FIGURE 38.8 Sex differences in the age of atrioventricular reentrant tachycardia (AVRT) onset. The age of AVRT onset is higher in men than in women (39.4 ± 18.0 years vs. 34.4 ± 16.5 years).

for ablation is in earlier age for the AVRT than it is for the AVNRT [1]. If patients present with symptoms before the age 30 years, the condition correlates with a 70% incidence of AVRT in men and 80% incidence of AVNRT in women. Onset of palpitations after the age of 30 years relates to AVNRT in 85% of patients regardless of sex [22].

Sources do not provide any proof of sex-related differences in data relating to interventional therapy. Total fluoroscopic and total procedure time of catheter ablation, acute success rate, complication rates including complete atrioventricular block, cardiac tamponade, aortic dissection, peripheral vascular embolism, coronary spasms, and ruptures of the coronary sinus seem to be similar between the sexes; so is the need for a second ablation procedure [23].

Sex-related differences were detected in analyses of the disease-specific questionnaires covering frequency and duration of SVT episodes, type and severity of symptoms, medication, and other parameters as health-related quality of life. Overall women stated more subjective symptoms than men not only during the period before catheter ablation but also after the procedure. Symptoms in women did not resolve as quickly after radiofrequency ablation as they did in men. Before the catheter ablation, women mostly complained of palpitations, while men experienced syncope. When comparing the improvement in the frequency of symptoms before and after the procedure, women felt lesser improvement subjectively, as if the average length of SVT episode was reduced from duration in minutes at baseline to a couple of seconds after the catheter ablation. However, objectively, there was no arrhythmia detectable on the ECG. In men, however, the frequency of SVT episodes decreased from about two per month to none and also the length of SVT episodes shortened from the duration of minutes to none. Concerning medical therapy, there are no significant differences in the prescription of β-adrenolytics and calcium channel inhibitors by sex. Antiarrhythmic drugs (propafenone, sotalol, or amiodarone) are more often prescribed to women than men in the period before catheter ablation [24].

More sex differences can be found in the therapeutic decision-making in SVTs. Despite women having more symptoms, they are referred to invasive therapy years later than men and also after failing more antiarrhythmic drugs. Women's symptoms are more often misinterpreted for anxiety, panic attacks, stress, or depression, and they receive antidepressive treatment instead of being referred for arrhythmological examination and following effective intervention. More women than men stated that they were not taken seriously when consulting medical professionals for their tachycardia symptoms [25]. On the other hand, real anxiety can complicate arrhythmias and may be an important factor to be considered in patients with paroxysmal SVT. It seems not to be dependent on different personality types. Female and geriatric patients suffer from anxiety more often, mostly in association with AVNRT [26].

Conclusion

AVRT is more common in men. Men have a higher prevalence of anterograde accessory pathway and more antidromic AVRT, which is associated with delta wave on surface ECG. Women statistically show not only more concealed and fewer manifest but also more multiple accessory pathways. Coincidence of paroxysmal atrial fibrillation in AVRT patients presents a potentially life-threatening condition.

The very fast atrial fibrillation tachycardia can, in some cases, send the stimulus through the accessory pathway, and this may lead to ventricular fibrillation and sudden cardiac death. The location of accessory pathway is sex-dependent. Some studies show no significant difference in left free wall (which is most common) and posteroseptal location. The right free wall location seems to be more frequent in females and the right anteroseptal location is more frequent in males, but the literature data are not completely consistent. The age of tachycardia onset is lower in women. There are no significant differences in catheter ablation therapy outcomes, but premenopausal women show cyclic variations of tachycardia episode occurrence and also inducibility and ablation success depending on the ovarian cycle phase, probably in correlation with sex hormones production. Women are more symptomatic than men not only in the period before catheter ablation but also after the procedure, and symptoms do not resolve as quickly after radiofrequency ablation as in men. Women's symptoms are often incorrectly interpreted; they are treated with more antiarrhythmic drugs before invasive diagnostic, which results in delay of catheter ablation therapy.

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Chapter 39

Sex and cardiac electrophysiology: atrioventricular nodal reentrant tachycardia

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Background

In adults, atrioventricular nodal reentrant tachycardia (AVNRT) is the most common paroxysmal supraventricular tachycardia (SVT) [1]. The median symptom onset occurs at 31 years of age (ranging 5−77 years) [2]. In the general population, the prevalence of AVNRT occurred in 22.5/10,000 persons and at an incidence of 35/100,000 person years [1]. First-degree relatives of those with AVNRT have a 3.6 times higher rate of AVNRT than those in the general population [1]. Despite familial clustering of arrhythmia, no single gene or gene family has been identified [3]. In one study which included 203 patients undergoing electrophysiology (EP) study and catheter ablation, the mean age at time of the procedure was 52 years [4].

AVNRT occurs more often in women than men with a prevalence 2:1 [5] (Fig. 39.1). Although the prevalence of dual atrioventricular (AV)-nodal pathways is equal in men and woman, women have shorter refractory periods present in their slow pathway, increasing the window for AVNRT induction [5,6]. During a study of 203 patients undergoing EP study and catheter ablation, women were younger than men, women without heart disease typically experienced their first episode prior to menopause, and men had a greater incidence of structural heart disease which included ischemic heart disease, aortic insufficiency, aortic stenosis, aortic valve disease, aortic valve prosthesis, atrial septal defect, and chronic heart failure [4].

Sex-based differences in incidence and timing of presentation of arrhythmias

Many structural and electrophysiologic properties of the heart display variances between sexes. Anatomical differences in women include a smaller heart and chamber size when compared to men [6]. Females on average have higher resting heart rates compared to men [6,7]. Women's heart rates are typically three to five beats faster than men which persist after administration of autonomic blockades such as propranolol and atropine [6−8]. Women also have shorter QRS complexes and smaller QRS voltages [6].

Both cytoplasmic and nuclear receptors for sex hormones are found on various cardiovascular tissues [7]. Sex steroids affect electrophysiological properties of myocardial cells and as such can explain some of the variance in arrhythmia risk and presentation [7]. There are no sex-based differences in QTc intervals during childhood, yet during adulthood QTc-interval differences are present [7]. For example, QTc intervals are equal until boys reach puberty and then their QTc interval shortens [6,7]. As boys age, their QTc interval does gradually lengthen yet remains shorter than the QTc of women [6,7]. In clinical practice, QTc intervals are adjusted for sex with QTc upper limits for males 450 ms and 460 ms in women [6]. Estrogen can mimic calcium channel antagonists by prolonging repolarization. Progesterone can impact cardiac repolarization via nongenomic pathways and testosterone shortens QT intervals [5]. SVT episodes have been found to increase during the luteal phase of the menstrual cycle in women, a period in which progesterone levels gradually increase as well as the progesterone/estrogen ratio [6,7]. Menopause is another time when women experience hormonal changes which may increase SVT episodes [5].

Differences between sexes can be found with many cardiac diagnoses. For example, sudden cardiac death, atrial fibrillation, ventricular fibrillation, atrioventricular reciprocating tachycardia (AVRT), and Wolff−Parkinson−White syndrome all occur more often in men

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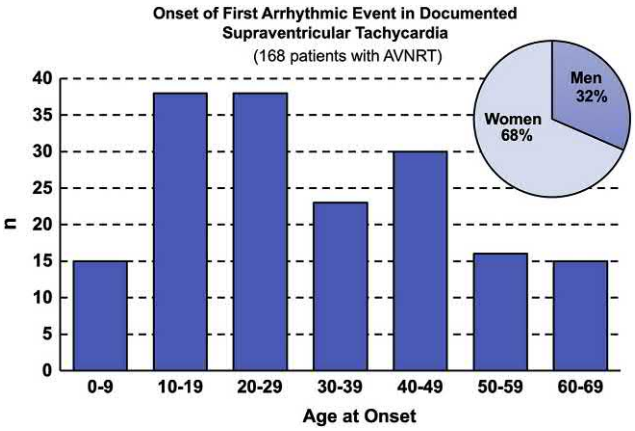

FIGURE 39.1 Age of onset of symptoms related to atrioventricular nodal reentrant tachycardia (AVNRT) and sex-based differences in prevalence [9].

[4,6,7,9]. Women, however, are more likely to have drug-induced Torsades de pointes, long QT, atrial tachycardias, and AVNRT [4,6,7,9]. From a mechanistic standpoint, administration of estradiol prolongs the duration of action potential, and dihydrotestosterone affects the early repolarization in ovariectomized rabbits [7]. AV conduction differences in women include their shorter atrial-His (AH) and His-ventricular (HV) intervals [6]. Women have shorter AV nodal effective refractory periods (ERPs), yet there are differences in fast pathway ERP between sexes [4]. Women have an increased incidence of SVT diagnoses, exacerbations, and symptoms during pregnancy and the early postpartum period which has been hypothesized to be multifactorial related to hormonal factors, autonomic tone, and increased intravascular tone [7].

Mechanisms of AVNRT

AVNRT is a reentrant tachycardia dependent on the unique refractory period of the AV nodal tracts broadly termed the fast and slow pathways. The presence of both pathways on an electrocardiogram (ECG), or during an EP study, has been termed dual AV nodal physiology. Many electrophysiologic changes occur within the heart over a person's lifetime—some of which involve the AV node and its conductive properties. Dual AV nodal physiology incidence increases over time and AV nodal refractoriness prolongs as children and adolescents age [4]. Gradual structural and geometric changes may occur in the AV node and its transitional zone between pathways until the age of 20, at which time an age-dependent increase in dual AV nodal physiology is observed [4,10].

AVNRT itself uses different mechanisms to allow the tachycardia to initiate. The most common form of AVNRT uses slow to fast (97%) versus fast to slow (3%) pathways for the circuit [9]. During an episode of SVT, changes in atrial contraction timing relative to ventricular systole result in hemodynamic instabilities [2]. AVNRT typically occurs in a spontaneous pattern related to critically timed spontaneous or triggered ectopy with mean tachycardia heart rates of 178 bpm [2].

Sex-based differences in AVNRT mechanisms and risks

In a study of 203 patients who examined sex-related differences in AVNRT, 139 were women. All patients underwent EP study and catheter ablation for AVNRT. The mean age of the population was 52. Women were younger and also had less ischemic heart disease, aortic insufficiency, aortic stenosis, aortic valve disease, aortic valve prosthesis, atrial septal defect, and chronic heart failure when compared to men [4]. This study highlighted sex-based variances in presentation timing and incidence.

We know that with or without clinical arrhythmia, women have shorter sinus cycle lengths, HV intervals, AV block, slow pathway ERP, and tachycardia cycle lengths [4,6,7]. As women have on average shorter AV nodal ERPs with similar fast pathway ERPs as men, they have a larger window of risk that may explain the unique sex-based vulnerability to the arrhythmia (Fig. 39.2) [4]. The enhanced window of vulnerability can be unmasked in women during increased arrhythmia susceptibility when progesterone levels increase and/or estradiol levels decrease [11].

Arrhythmia presentation and diagnosis

Reported symptoms include palpitations, dyspnea, lightheadedness, diaphoresis, chest pain, and anxiety [2]. These symptoms typically occur later in life in those with AVNRT versus AVRT [5]. Symptom onset commonly occurs at a younger age in those without structural heart disease [4].

In regard to variance of symptoms between sexes, AVNRT is the most common SVT mechanism when symptoms are reported in women older than 10 years of age. Symptoms of AVNRT are reported at a younger age in females versus men [5]. In a population of patients who received an EP study for AVNRT, women without heart disease were more likely to experience their first episode of tachycardia during traditional childbearing ages. This pattern shifts to a later presentation in women who over time develop heart disease [4].

Diagnosis of AVNRT is suggested by a short RP SVT morphology and is confirmed during EP study. The transient nature of arrhythmia can mimic anxiety attacks. Symptoms commonly described by patients with SVT can fulfill the formal psychiatric criteria for panic disorder. This

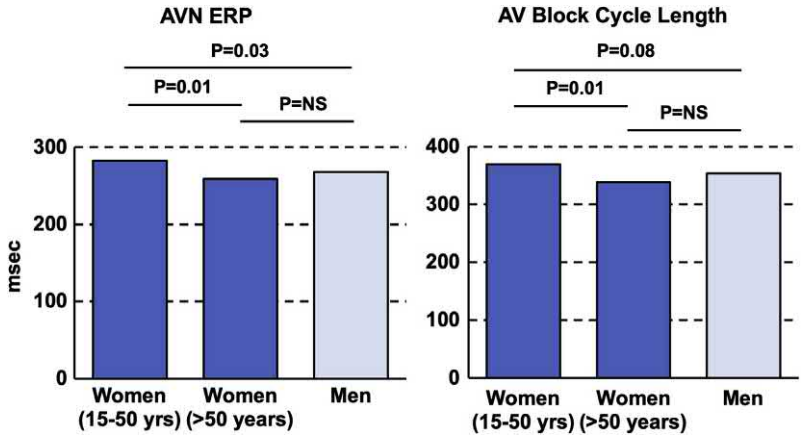

FIGURE 39.2 An illustration of a comparison of atrioventricular (AV) nodal effective refractory period (ERP) and AV block cycle length (msec) study between women of childbearing age (15–50 years), older women (>50 years), and men. *Adapted from Liuba I, Jonsson A, Safstrom K, Walfridsson H. Gender-related differences in patients with atrioventricular nodal reentry tachycardia. Am J Cardiol 2006;97:384–388.*

can potentially lead to misdiagnosis and delay in SVT treatment [5]. Misdiagnosis may then lead to the administration of inappropriate medication treatment and delayed SVT treatment. It has been shown that women are more likely than men to be misdiagnosed with panic disorders by providers and SVT symptoms may be attributed to panic, anxiety, or stress [2]. In general, ruling out a potential arrhythmia mechanism is critical before confirming panic attack, given the overlap of symptoms and often misclassification, particularly in women [2,5]. Due to the unpredictable nature of the arrhythmia, ambulatory event monitors are more effective than Holter monitors when capturing these episodes [2].

Sex variance in management approach

Pharmacologic therapy

In consideration of pharmacologic therapies, women are at higher risk of developing Torsades de pointes when exposed to medications that prolong the QT interval. It has been recommended that women requiring chronic class IA or III antiarrhythmic drug therapy should receive regular clinical assessment and ECG monitoring [12]. Risk is further magnified in elderly females due to the potential of drug–drug interactions and decreased renal function [12].

The shorter QT intervals in men are noted after puberty during which there is higher exposure to androgens. The short QT interval is maintained during slower heart rates in men, often protecting them from Torsades de pointes from reverse use–dependent drug therapy [12].

Nonpharmacologic therapy

Ablation is often the treatment of choice for AVNRT and it is the only cure for the arrhythmia [2,8]. Women tend to have had symptoms longer than men and try more antiarrhythmic medications prior to SVT ablation. It takes women a mean of 5 years longer than men to undergo invasive treatment from onset of their palpitations. This reflects the more conservative approach and difference in clinical presentation in women versus men. It is possible that the timing of the onset of symptoms is typically during childbearing age, and the radiation generally used during invasive procedures would lead to postponing treatment [13]. These data also highlight likely important disparities in the management of heart disease in women compared to men. In general, treatment for both men and women should be similar with exceptions for women during pregnancy and caution for QT prolongation risk.

Since SVT incidence increases during the luteal phase of the menstrual cycle, when concentrations of progesterone concentrations are highest, invasive EP studies should be timed during the second half of the menstrual cycle to improve SVT inducibility [5,6]. Women have increased success of SVT induction via EP studies midcycle. This was shown to be true in one study where women without successful AVNRT induction during their first EP study had successful AVNRT induction when they underwent repeat EP studies during menstruation [7,10]. Men and women have comparable efficacy, complication, and recurrence rates when undergoing SVT radiofrequency ablations [5,7].

Pharmacologic and nonpharmacologic therapies during pregnancy

During pregnancy, treatment of arrhythmias should be based on how frequent and how severe symptoms occur. For women, pregnancy can be a proarrhythmic state often resulting in the first episode or more frequent episodes of AVNRT. This is thought to be caused by hormonal and hemodynamic changes which occur during the pregnancy

[12]. When treatment is required during pregnancy, medical management may be the treatment of choice until the mother delivers, to minimize procedural risk to the mother and fetus [7]. When using medications during pregnancy, providers should wait until after the first trimester whenever possible to use medications since organogenesis is relatively complete at that time making many drugs safer to the fetus. Providers should then use the lowest effective dose combined with frequent ECGs for monitoring [12,14]. The Food and Drug Administration has placed a class to medications which indicates risk to the fetus when used during pregnancy [12]. Class B indicates the effects are unknown to the fetus [14]. Class B antiarrhythmic medications include lidocaine, pindolol, and sotalol. When possible, they should be chosen over class C medications. One exception is adenosine with, although it is considered a class C medication, its short half-life of 10 s should limit its effects to the fetus. Class C indicates the risk to the fetus cannot be ruled out. Class C antiarrhythmic medications include quinidine, procainamide, disopyramide, mexiletine, flecainide, propafenone, dofetilide, verapamil, propranolol, metoprolol, digoxin, and adenosine. Class D indicates that there has been evidence of fetal risks with use. Class D antiarrhythmic medications include amiodarone and atenolol. Category X drugs have been shown to have teratogenic effects and therefore are contraindicated to use during pregnancy. There is only one category X antiarrhythmic medication which is dronedarone.

Beta blocker use in pregnancy has been shown to result in fetal growth retardation with the use of atenolol during the first trimester. Propranolol and metoprolol are commonly used in women during pregnancy for other cardiovascular conditions with favorable long-term data, and therefore can be used when necessary during pregnancy [12]. Radiofrequency ablation should be recommended prior to future pregnancy due to the known increased incidence of SVT exacerbations and symptoms [7,12]. Radiofrequency can be done during pregnancy but should be done without fluoroscopy with trimester-dependent risk assessment for anesthesia [15].

Conclusions

Important differences between sexes exist in the risk, presentation, and treatment of AVNRT. A summary of these is displayed in Fig. 39.3. Women are at higher risk of developing the arrhythmia and present earlier with symptoms; however, treatment is often delayed. Delays in treatment reflect misdiagnosis and likely underuse of non-pharmacologic therapies, despite similar efficacy and safety profiles between sexes. Long-term pharmacologic management can be considered, but in women there exists a higher risk of QT prolongation and a need for closer follow-up to minimize risk of proarrhythmia.

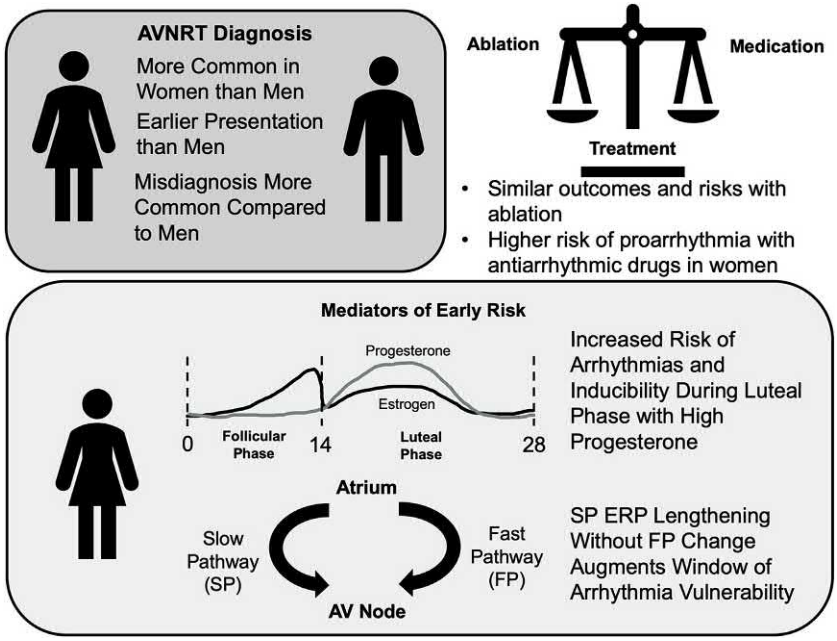

FIGURE 39.3 Summary of differences between sexes that exist in the risk, presentation, and treatment of atrioventricular nodal reentrant tachycardia (AVNRT).

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Chapter 40

Inappropriate sinus tachycardia

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Introduction

Inappropriate sinus tachycardia (IST) is a relatively rare clinical syndrome of nonparoxysmal elevated resting heart rate (HR) >100 beats per minute or an average rate >90 bpm measured by 24-h ambulatory monitor. Ambulatory monitoring in IST patients may reveal several different HR patterns: persistent HR elevation with a resting or mean HR >95 bpm, moderately elevated resting HR >85 bpm with exaggerated response to minimal exertion, or normal resting rate with an exaggerated HR response to exercise. By definition, IST occurs in the absence of physiologic demand (secondary causes). Patients with IST may present with or without symptoms. In the presence of symptoms, the term IST syndrome is used.

Symptoms in patients with IST can be variable including palpitations, fatigue, and sensation of a racing heartbeat. The P-wave morphology and axis on a standard 12-lead ECG during tachycardia should be similar to sinus rhythm. The prevalence of IST is incompletely defined due to incomplete sampling, reporting, and absence of symptoms in some patients.

There are clear sex discrepancies between IST patients. It is clinically recognized that a disproportionate number of symptomatic IST patients are female with a variable age range of 18—50 years of age. There are several theories of the mechanistic etiology of IST, which can be categorized as either *intrinsic* or *extrinsic*. The purpose of this chapter is to review normal sinus nodal physiology and the different proposed mechanisms of IST including the clinical presentation, treatment methods, and overall prognosis.

Sinoatrial node anatomy and function

The sinus node (SN) has unique anatomical structure, which relates to its function. Understanding this aspect of the SN is important for IST recognition, differentiation, and treatment.

Anatomical consideration

The sinoatrial node is a differentiated region of specialized conduction tissue in the right atrium. This complex tissue unit resides at the junction of the crista terminalis (CT) and venous tissue in the intercaval region (between the superior and inferior vena cava) [1]. The location can vary between species as can the cross-sectional anatomical design. In humans, the SN lies under a thin layer of atrial myocytes and does not comprise the total cross-sectional atrial tissue as in other mammals including rabbits.

The tissue unit itself can be easily identified in atrial dissection due to the unique cellular features comprising the SN. The cells are highly compacted in a dense network of fibroblasts and pacemaker/nodal cells. The cells are thin (5—10 μm in diameter) and elongated/spindle shaped (25—30 μm long), and the intracellular structure reveals a lack of extensive myofibrils when compared to myocytes. Due to the lack of lower metabolic requirements, they have fewer mitochondria but are rich in membrane invaginations called caveolae. Surrounding the compact node, there is a gradual transition of cells from the compacted nodal cells to cells with increasing density of myofilaments and mitochondria (transition cells), to regular atrial myocytes in the region around the compact node. Nodal cells are electrically coupled by gap junctions although the exact molecular make-up of that structural connection and density of gap junctions is not clear in humans. In general, the electrical coupling is thought to be less than in atrial cells and manifest with slower conduction velocity in the SN. The electrical signal transmission from the compact node to the atria is achieved via a gradual interdigitation of nodal cells with transition cells and atrial cells, which have an increasing complexity of connexin staining suggesting increased gap junction cellular connections.

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Functional action

Activation sequences

The exact characterization of human SN is more difficult because overlying atrial myocytes interfere with electrical mapping efforts. Therefore, comparisons with more well-studied small mammals are considered reasonable particularly in rabbits where SN propagation appears to be similar. In the rabbit, the electrical connection of the SN to the atria is limited to promote a unidirectional action potential front with propagation initiating in the compact nodal center and extending oblique and caudal toward the CT. The leading pacemaker site is generally in the center of the compact nodal cells, 0.5−2 mm from the CT. The conduction velocity is slow at 2−8 cm/s and depends on the direction of propagation with faster conduction noted when the impulse propagation is parallel to the CT when compared to perpendicular. The peripheral zone containing increasing density of transition cells is faster at approximately 35−50 cm/s, again with faster conduction parallel to the CT. On the septal edge of the wavefront, the signal is blocked either functionally or physically with nonconducting connective tissue. One theory of why this occurs is to prevent dilution of the signal by suppression from surrounding tissues or reentry from action potentials outside the SN. In theory, this will maximize the pacing source to avoid a source-and-sink mismatch. Thus, as the wavefront propagates, it is broad, unidirectional, and as it picks up speed, it is capable of driving the atrial muscle tissue in depolarization.

Action potential

The SN represents slow response tissue, which has different properties from the fast response tissues such as atrial and ventricular myocytes. Phase 0 depolarization depends on an inward calcium (not sodium) current via L-type calcium channels, which have a slower conduction velocity than the sodium channels with longer activation time. In line with the activation sequence, the action potential duration is longest in the slow conducting cellular regions. Like other regions and cells in the heart (such as Purkinje fibers and ventricular muscle), repolarization occurs in the opposite direction to depolarization, thus inhibiting reentry.

The distinguishing functional feature of sinus nodal tissue is the dominance of phase 4 diastolic depolarization. Slow increase in membrane voltage (phase 4) until the voltage reaches L-type calcium channel voltage of activation results in firing of the next action potential (see Fig. 40.1). Phase 4 diastolic depolarization occurs via the "funny" current or I_f and is a dominant feature of sinoatrial nodal tissue. Inward I_f is activated with polarization of the membrane potential to −40 to −45 mV [2]. Inward I_f terminates when the voltage threshold for the L-type Ca^+ channel is reached and subsequent depolarization occurs. Because the reversal potential (at which point I_f is outward) is −10 to −20 mV, there is a brief interval during depolarization when it carries an outward component at these more positive voltages. These inward and outward components are due to the mixed Na^+/K^+ permeability of I_f channels. The molecular correlate for I_f is HCN channels. There are four isoforms of HCN found in the heart and the dominant isoform in the SN is HCN4. Expression of HCN4 is dense in the compact node and diminishes to negligible quantity in the surrounding atrial myocytes.

The exact initiation of pacemaker activity is a subject of some debate [3,4]. The membrane mechanism relates to the electrophysiologic characterization of I_f and its capability of

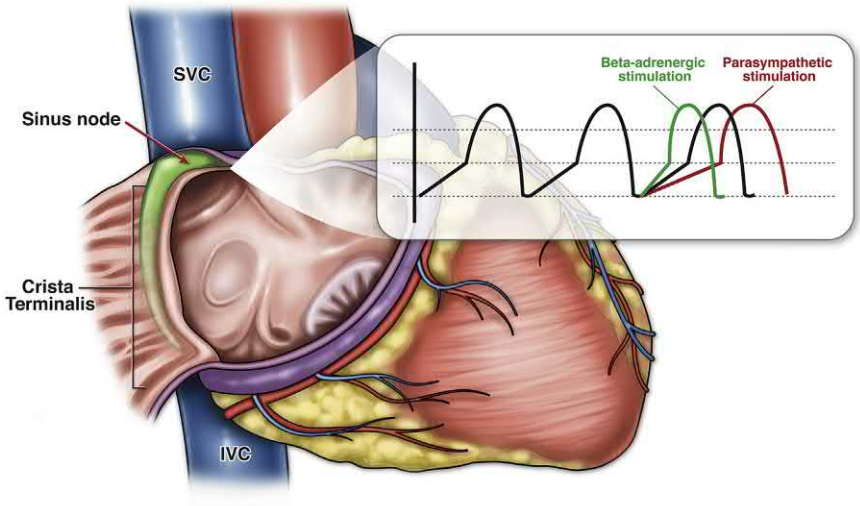

FIGURE 40.1 Schematic of the sinus node in the right atria. Nodal action potential: note dominant phase 4 depolarization and dynamic changes with autonomic regulation.

generating inward diastolic depolarizing current in phase 4. There is also a proposed role generated by inward depolarizing current from the sodium–calcium exchanger (NCX) in response to submembrane cyclical Ca^{2+} release from the sarcoplasmic reticulum, the so-called "Ca^{2+} clock." Autonomic regulation of both systems appears to work in concert with both the membrane and Ca^{2+} clock mechanisms, and more recent theories revolve around coordination of the mechanisms rather than exclusion of one mechanistic theory or the other.

Regulation

Autonomic regulation represents the major modulators of the SN (see Fig. 40.2, from Olshansky *JACC* 2013; 61:793–801). Both beta-1 and beta-2 adrenergic receptors occur in SN cells and there is dense sympathetic innervation. This provides capability for both circulating and local adrenergic agonists to regulate the SN. Specifically, HCN channels are modulated by beta-adrenergic receptors through cAMP phosphorylation that shifts the activation potential positively and accelerates the slope of phase 4 depolarization. HCN phosphorylation by Src/tyrosine kinase accelerates channel activation to a more positive voltage similar to cAMP.

The SN is also innervated by the vagus nerve and contains a rich supply of acetylcholine receptors. Activation of the vagus nerve or application of acetylcholine (in experimental preparations) causes a slowing of the rate of depolarization with a reduction of the slope of phase 4 depolarization. Experimentally it has been shown that ryanodine, which binds to ryanodine receptors to permit

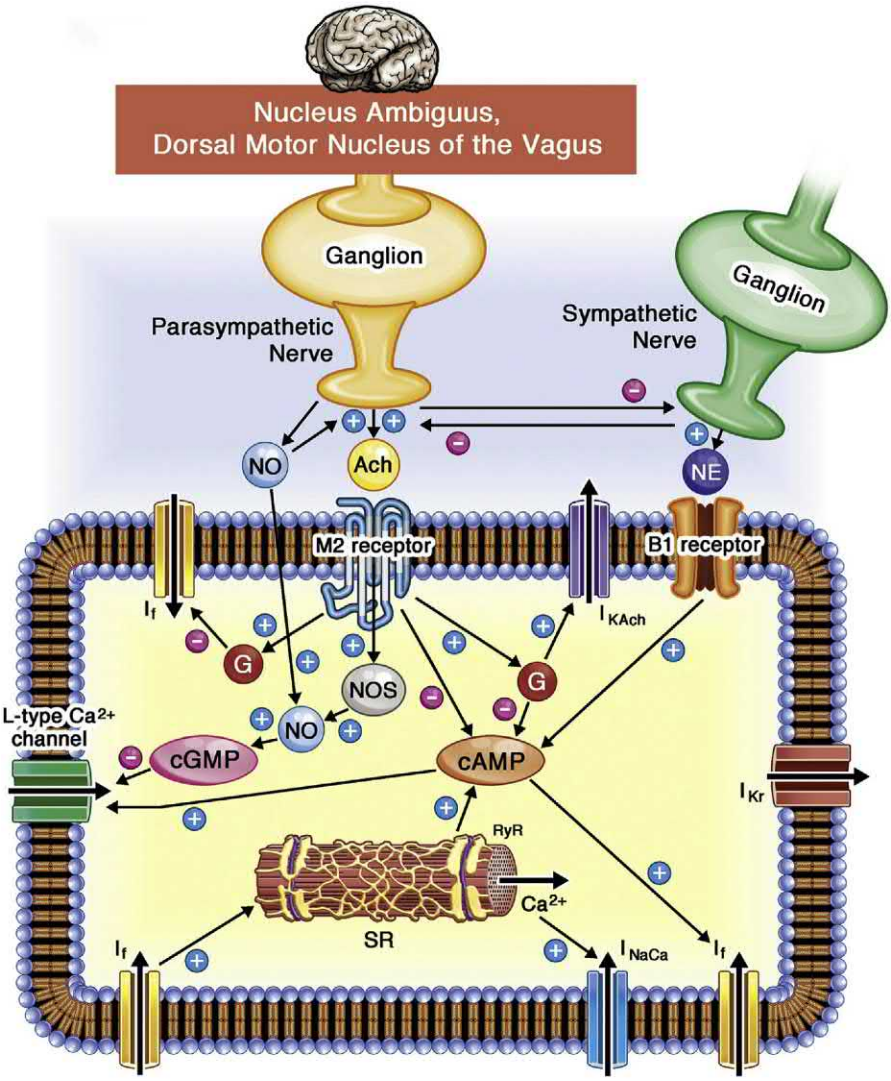

FIGURE 40.2 Autonomic nervous system regulation of heart rate. *From Olshansky B, Sullivan RM. Inappropriate sinus tachycardia. J Am Coll Cardiol 2013;61(8):793–801.*

calcium extrusion from the sarcoplasmic reticulum, causes an "unloading" of the sarcoplasmic reticulum calcium stores that inhibits further calcium transients and thus blocks subsequent depolarization.

Intrinsic heart rate measurements

Comprehensive studies of broad populations of healthy controls have been used to define the normal intrinsic heart rate (IHR). IHR is defined as the HR in the absence of autonomic influence [5]. 432 volunteers (hospital staff and students, inmates from penitentiary) were enrolled who were not taking significant medications, had no fever, and no history of heart disease. To record the IHR, autonomic blockade using propranolol 0.2 mg/kg and atropine 0.04 mg/kg were given intravenously. IHR absolute values ranged between 78 and 126 bpm averaging 103.6 bpm and were inversely proportional with age. There were no differences in IHR between males and females in any age group. According to their study, IHR can be calculated: IHR = 118.1—(0.57xAGE). This was confirmed by another study by Ref. [6] who measured IHR following autonomic blockade with propranolol 0.2 mg/kg and atropine 0.04 mg/kg in 20 individuals (11 male and 9 female) during an invasive electrophysiologic studies 2 days sequentially. The mean IHR was 103 ± 13 bpm in those <45 years of age and 93 ± 8 bpm in those >45 years of age. All individuals had IHR greater than resting HR and were within the range of the formula derived by Jose and Collison in 1970.

IST mechanism

The mechanistic etiology of IST is the subject of debate and remains unsettled. Several mechanisms including excessive sympathetic or reduced parasympathetic drive, excessive IHR, dysfunctional neurohormonal modulation, ectopic activity of the SN, and beta-adrenergic receptor autoantibodies are proposed. Some data report an abnormal response to autonomic stimulation due to tissue/cell level changes (*intrinsic* mechanism), while other data suggest that there is a disruption of the autonomic stimulation itself with normal tissues/cell level findings (*extrinsic* mechanism). It is possible that both mechanistic theories are correct because despite sharing a single common pathway of sinus tachycardia, the underlying mechanistic etiologies between individual patients may differ.

Intrinsic

One mechanistic etiology of IST is referred to as an intrinsic mechanism. In 1994, Morillo et al. provided an in-depth phenotypic evaluation, IHR measurement, and autonomic balance of a small series of IST patients (all female) compared to control group. An infusion of propranolol (0.2 mg/kg) and atropine (0.04 mg/kg) was used to achieve pharmacologic autonomic denervation to measure the IHR. The IHR was 2 standard deviations higher than formula predicted value (see IHR section above), and has been corroborated by several other studies including Ref. [7,11]. The observations of Ref. [11] can be appreciated from Fig. 40.3 indicating an increased resting HR and IHR. These authors hypothesized that this pointed to an intrinsic abnormality of the SN. In the Morillo et al. study, the IST group demonstrated an exaggerated response to beta-adrenergic stimulation and in contrast a depressed response to cardiovagal stimulation, Fig. 40.4.

Enhanced or exaggerated sympathetic response has recently been reported to be due to an increased cAMP response from a rare HCN4 mutation. Baruscotti et al. performed functional studies from this HCN4 mutation and showed a gain of function, which is in contrast to the loss-of-function HCN4 mutations causing bradycardia and SN dysfunction [9]. The reported gain of HCN4 function

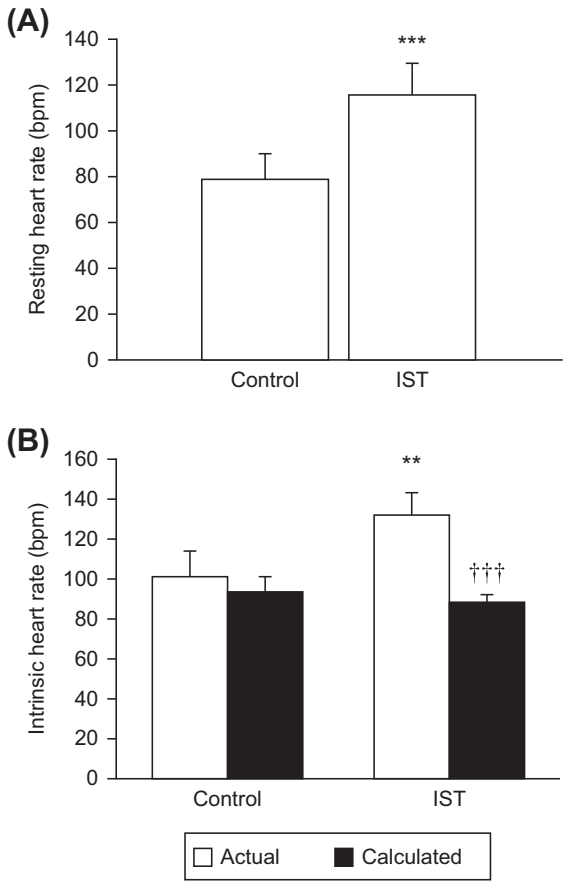

FIGURE 40.3 Resting heart rate and IHR in IST compared to control. (A) Resting heart rate and (B) IHR in IST compared to control. *From Still AM, Huikuri HV, Airaksinen KE, Koistinen MJ, Kettunen R, Hartikainen J, Mitrani RD, Castellanos A, Myerburg RJ, Raatikainen MJ. Impaired negative chronotropic response to adenosine in patients with inappropriate sinus tachycardia. J Cardiovasc Electrophysiol. 2002;13:557–62.*

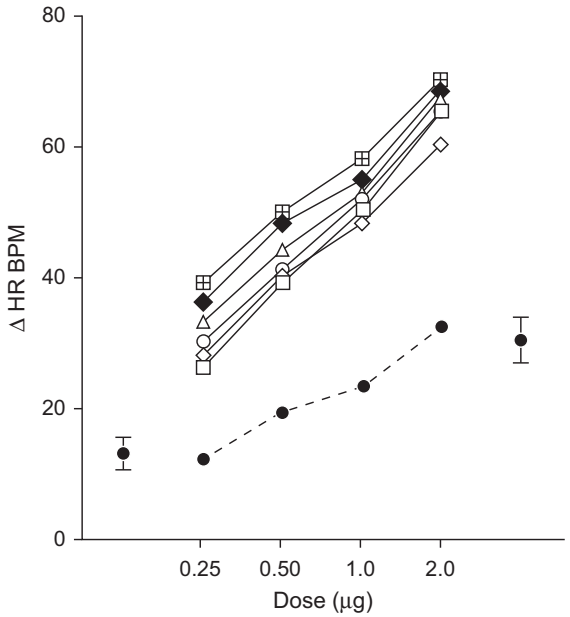

FIGURE 40.4 Exaggerated beta-adrenergic response in IST compared to control. *From Morillo CA, Klein GJ, Thakur RK, Li H, Zardini M, Yee R. Mechanism of 'inappropriate' sinus tachycardia. Role of sympathovagal balance. Circulation. 1994;90:873–77; Fig. 2.*

mutation is located in the cyclonucleotide-binding domain (CNBD) where cAMP binds to HCN4. Expressed in heterologous expression system, the HCN4 mutation causes channel activation at more depolarized voltages and increased cAMP sensitivity. This same mutation expressed in murine neonatal cardiomyocytes is associated with an increased intrinsic heart rate and a shift in activation voltage to more depolarized voltages.

The endogenous purine nucleoside adenosine has several antiarrhythmic effects and is known to slow sinus rates, particularly with higher atrial rates. Still et al. demonstrated that in IST patients, sinus rates were only minimally slowed even at the maximum adenosine dose regardless of autonomic tone. Moreover, IST patients exhibited an impairment of the negative chronotropic action of adenosine, which was surprising given the rate-dependent action of adenosine. In that study, the authors concluded that with the impaired response to adenosine, excessive sympathetic input seemed less likely to be the primary mechanism and suggested an intrinsic malfunction of the acetylcholine- and adenosine-sensitive potassium channel.

Extrinsic

In contrast to the intrinsic mechanism, the extrinsic theory of IST relates to evidence supporting an extrinsic increased sympathoexcitation or decreased parasympathetic activity. In a study published in 1998 by Castellanos et al., IST patients were studied with 24-h Holter monitor and compared to a control group [15]. HRV indices were studied including the mean RR interval, the standard deviation from the mean of RR interval, and the standard deviation of 5-min mean standard deviation of RR intervals. Using both these time and frequency domain indices, IST patients demonstrated a reduction in the HRV compared to the control group suggesting a decrease in parasympathetic activity. Likewise, an investigation of middle age and older IST patients by Lopera et al. showed similar reduction in HRV in this older population compared to control [16]. The baroreflex function has also been evaluated in IST patients in several studies. Leon et al. showed that IST patients demonstrated a lower baseline supine baroreflex gain and a blunted response to orthostatic stress when compared to a control group [10]. Furthermore, time domain analysis of HRV seemed to suggest reduced vagal tone both at rest and in the upright position. These findings are probably due to a shift in the baroreceptor threshold and operational point and could explain the elevated HR despite having a higher BP when compared to healthy subjects.

The etiology behind decreased parasympathetic activity may have its roots in the production of autoantibodies to ganglionic acetylcholine receptors. Vernino et al. described a high specificity (although low sensitivity) of ganglionic receptor–blocking antibodies or ganglionic receptor–binding antibodies in idiopathic autonomic neuropathy patients [12]. Similarly, Chiale et al. found a high prevalence of anti–beta-receptor antibodies in ~50% of a small IST cohort which caused a long-lasting enhancement of cAMP [13]. However, in contrast to the Vernino study, no anticholinergic receptor antibodies were found.

Field et al. presented evidence in support of an extrinsic mechanism for IST in a study comparing IST versus atrial tachycardia versus control patients receiving isuprel during invasive EPS [14]. Knowing that the normal physiologic response of the SN to sympathetic stimulation is an increase in P-wave amplitude in the inferior leads (shift of the dominant pacemaker superiorly on the CT) and shortening of the PR interval due to accelerated AV conduction, the authors hypothesized that similar changes should be seen in IST patients at faster rates if the mechanism is extrinsic. Conversely, the P-wave amplitude should remain the same if the mechanism is intrinsic and the PR interval should lengthen at faster rates similar to what is seen in patients with focal atrial tachycardia. The authors found that in IST patients, P-wave amplitude and PR interval changes at faster rates mirrored the changes observed in the control group following isuprel administration (Isuprel Group), supporting an extrinsic mechanism (see Fig. 40.5).

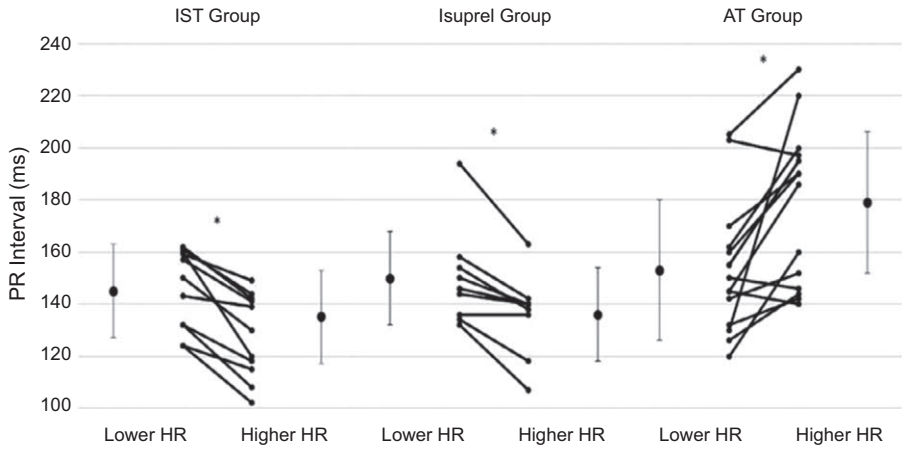

FIGURE 40.5 PR-interval assessment. *Adopted from Field ME, Donateo P, Bottoni N, Iori M, Brignole M, Kipp RT, Kopp DE, Leal MA, Eckhardt LL, Wright JM, Walsh KE, Page RL, Hamdan MH. P-wave amplitude and pr changes in patients with inappropriate sinus tachycardia: findings supportive of a central mechanism. Journal of the American Heart Association. 2018;7. https://doi.org/10.1161/jaha.118.008528.*

Sex differences

Nonsystematic clinical observation suggests that IST is more common in young women particularly those in health care; however, determining the prevalence of IST is challenging because some individuals do not have associated symptoms. Using the definition of average HR >90 bpm on 24 h with no primary causes [17] estimated a prevalence of 1.16% in 604 individuals evaluated for hypertension (age 40−59). Of note, the resting blood pressure was higher in IST subjects compared to non-IST subjects. There was no sex difference between the groups; 57% of the subjects were women in the IST group compared with 56% in the control group. In the same study, the authors evaluated the natural history in another group of patients with symptomatic IST. Unlike the random group, 89% of patients with symptomatic IST were women. This study mirrors other observational data suggesting that women are more symptomatic with IST than men. The reason behind this observation is unclear and postulated hypotheses have been unexplored. If the autoimmune−based mechanistic theory is correct, this may explain the sex discrepancy because women have more frequent autoimmune disease. However, it should be noted that the available studies of IST are of very small cohort size and therefore a detailed subanalysis based on sex is not statistically valid.

Clinical presentation

Patients with IST present in a variable manner with some asymptomatic identified incidentally during a routine exam and others experiencing severe and disabling symptoms (IST syndrome). Common symptoms include the sensation of a racing heart at rest or with activity, palpitations, exercise intolerance, presyncope/syncope or multisystem, and nonspecific complaints such as fatigue, headache, abdominal pain, myalgia, depression, and anxiety. Secondary causes of sinus tachycardia should be considered before IST diagnosis can be made including fever, anemia, infection, and endocrine abnormalities. Blood tests to rule out secondary causes include complete blood count (anemia), fasting blood glucose (diabetic neuropathy), and thyroid function (hyperthyroidism). Other tests to consider include orthostatic norepinephrine, 24-h urine metanephrine excretion to rule out pheochromocytoma, and specific tests to rule out carcinoid, Cushing's, or other endocrinologic syndromes as deemed appropriate. Once secondary causes have been excluded, targeted autonomic testing and referral to a neurologist may be considered in selected patients suspected of having autonomic dysfunction.

Given the presence of sinus tachycardia and extracardiac symptoms, there is some diagnostic overlap between IST and postural orthostatic tachycardia syndrome (POTS) [18]. POTS is defined as an increase in HR of >30 bpm within 10 min of supine to upright posture change with symptoms in the absence of orthostatic hypotension [33]. Like IST, there is an observed female predominance with POTS from teenage to middle age years. POTS symptoms nearly always include lightheadedness and presyncope. Systemic nonspecific complaints are common and not always relieved with recumbent posture. The mechanistic etiology for POTS is unclear and may, like IST, stem from different mechanistic origins. In contrast to the persistently elevated HR seen in patients with IST, patients with POTS usually have a normal resting HR. In patients with IST, elevated HR is seen in response to emotional and physiologic stress, whereas in patients with POTS, the increase in HR is seen with orthostatic stress. General considerations for the differentiation of IST from POTS are included in

TABLE 40.1 Comparable differences between IST and POTS.

Table I	IST	POTS
Symptoms	**Frequently multisystem**	**Frequently multisystem**
Heart rate	Inappropriate for physiologic need	Upright tachycardia in the absence of orthostatic hypotension
	>90–100 bpm at rest or exaggerated response with minimal exertion ≥95 bpm mean	>30 bpm increase (frequently >120 bpm) within 10 min of upright position
Proposed mechanisms	Increased cardiac sympathetic receptor sensitivity	Autonomic neuropathy
	Increased cardiac sympathetic tone	Beta-adrenergic hypersensitivity
	Blunted parasympathetic tone in dead heart	Alpha-adrenergic hyposensitivity
	Regional autonomic dysregulation	Baroreceptor dysfunction
		Brainstem dysregulation
		Hypovolemia
		Venous pooling

Table 40.1. Note, there are some overlapping features suggesting a contiguous syndromic definition rather than a binary distinction.

Finally, an invasive EP study may be considered in some patients to differentiate IST from focal atrial tachycardia originating from the high CT, SN reentry tachycardia, or atrioventricular reentrant tachycardia. Occasionally patients may have both IST and supraventricular tachycardia, highlighting the importance of an invasive EP study and ablation to resolve some of the patients' symptoms. Maneuvers to differentiate these rhythms should be performed with careful attention to the P-wave morphology and pattern of HR responses. The presenting symptoms and clinical findings can be utilized to implement patient-specific treatment approaches.

Treatment

Treatment success for IST is dependent on a complete characterization of the clinical presentation and defining elements to establish the diagnosis and understand what needs to be addressed for each patient. Due to the overlap with other syndromes (see Fig. 40.6) and presence of extracardiac symptoms, the treatment should be aimed at managing both the tachycardia as well as the other clinical features.

IST patients with features of POTS, nonpharmacologic and exercise training and conditioning are key initial therapeutic interventions. Symptoms related to hypovolemia are in part due to venous pooling and reduced central blood volume and can be addressed with liberal salt and fluid intake and wearing compression garments. Structured exercise and endurance training called "physical reconditioning" have been demonstrated in multiple studies to relieve symptoms and improve quality of life with a similar or better compliance rate to drug treatment. The Heart Rhythm Society Expert Consensus Statement gives exercise training a Class IIa recommendation for POTS, see Ref. [19] for review.

Treatment approaches often require control of the HR or HR response to activity. Rate modulating drugs such as beta-blockers and nondihydropyridine calcium channel blockers have been used to decrease the resting and peak HR. However, IST-associated symptoms of presyncope and lightheadedness can be exacerbated by the hypotensive and vasodilatory response to these drugs at doses required to control HR. Additionally, the extracardiac symptoms occurring in IST including fatigue and depression can be worsened by beta-blocker treatment.

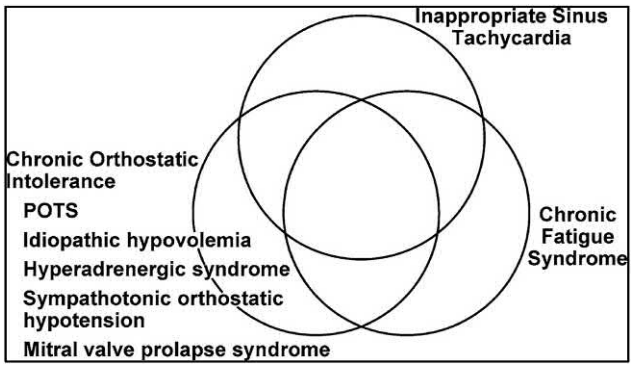

FIGURE 40.6 Venn diagram depicting the overlap of several clinical syndromes. *Modified from Brady PA, Low PA, Shen WK. Inappropriate sinus tachycardia, postural orthostatic tachycardia syndrome, and overlapping syndromes. Pacing Clin Electrophysiol. 2005;28:1112–21. https://doi.org/10.1111/j.1540-8159.2005.00227.x.*

A newer antiarrhythmic drug ivabradine was introduced clinically in Europe over 10 years ago and has revolutionized IST treatment [22]. Ivabradine modulates HR by blocking I_f and functions as an HCN open channel blocker (larger effect at high HRs). It was originally approved for use in unstable angina and it does not alter blood pressure nor is a negative inotrope. In a cohort study by Zellerhoff et al. 10 symptomatic female IST patients given (off-label) ivabradine had a reduced peak HR from a max of 176 ± 45 bpm to 137 ± 36 bpm and mean HR from 84 ± 11 bpm to 74 ± 8 bpm [20]. The use-dependent effect of the drug is notable in that patients with higher HRs had more significant rate modulation. IST-associated symptoms were significantly or completely relieved with ivabradine and no patients discontinued the medication due to side effects. In a separate Italian study of 18 symptomatic IST patients (16 female and 2 male) by Calo et al. [21], ivabradine was given twice daily at 5 mg and increased to 7.5 mg twice daily after 3 months if symptoms or elevated HR persisted. Holter data at 3- and 6-month time points demonstrated a significant decrease in the mean HR from 97.5 ± 4.7 bpm at baseline to 75.6 ± 7.5 bpm, and 67.6 ± 3.5 bpm, respectively. Similarly, max HR significantly decreased as did minimum HRs. Along with HR, symptoms resolved in all patients tolerating the medication and who completed the protocol at 6 months of follow-up (16 patients). A phosphene phenomenon was observed in one (1/18) patient who dropped out of the study due to medication intolerance. Self-resolving diplopia was observed but did not result in medication discontinuation Ref. [24] studied the adjuvant effect of ivabradine with metoprolol therapy. This non−placebo-controlled trial demonstrated both safety and efficacy of combination therapy for patients in whom monotherapy (with beta-blocker) was not effective.

In a double-blind placebo-controlled, crossover trial of ivabradine in symptomatic IST patients, Cappato et al. showed a significant decrease in mean, maximum, and minimum HRs in the 19 patients who completed the study (17 female) [23]. Exercise stress testing performed also indicated that ivabradine reduced peak HR and increased exercise duration and MET outputs, suggesting an increased cardiovascular performance. Similar to the non−placebo-controlled studies, patients had >70% of symptom resolution in this study and there was no difference in response to therapy based on sex.

An invasive treatment approach with SN ablation has been used by some investigators for IST patients who are refractory to medical therapy with beta-blockers or calcium channel blockers. Initial experimental studies in dogs in 1990s suggested that extensive ablation targeting the high CT could effectively ablate a desired region of the SN and shift pacemaker activity to a region lower on the CT without complete loss of pacemaker activity (SN "modification") [25]. In patients, administration of isoproterenol results in a cranial activation shift of SN activity along the CT. Targeting this region with ablation leads to a caudal shift and slower HRs [28]. Early adoption of this in patients resulted in low success rates and high complications rates including the need for permanent pacing, diaphragmatic paralysis, and SVC narrowing [29,30]. Moreover, in a small study of seven patients with IST and features of POTS, 5/7 had a successful SN modification and decreased HRs, but no resolution of symptoms [26]. The efficacy of ablation has improved with the use of 3D electroanatomic mapping in a relatively large study of 39 patients referred for SN modification [27]. However, due to the high recurrence rate and risk for procedural complications as well as the availability of an I_f blocker in most countries, ablation is no longer recommended in the routine care of patients with IST (Class III in the most recent HRS Consensus Statement).

Prognosis

Despite the concept that uncontrolled tachycardias can cause cardiomyopathy, it is interesting that IST is not associated with myopathic remodeling. Part of the definition of IST relies on the lack of structural heart disease. Indeed, in multiple cohorts of IST patients followed longitudinally, there was no evidence of myopathic remodeling. This is further evidenced by the study from Ref. [17] in which asymptomatic patients who were incidentally found to have IST for an unknown period of time lacked findings of structural remodeling. The overall benign IST prognosis provides further argument against invasive management by ablation which is associated with excessive risk. The favorable prognosis should not diminish the need for successful symptoms management since some patients have debilitating symptomatology. Assessment of overlapping clinical syndromes and patient participation are essential for successful treatment. This often requires a multidisciplinary approach, as HR control alone often does not address all the symptoms in patients with IST.

Conclusions

IST is a rare disorder with an apparent female predominant prevalence in the symptomatic population. While there are sex differences in prevalence, it is unclear if true sex differences in mechanism(s) exist. Successful management requires treatment approaches directed toward specific symptoms/overlapping syndromes as well as HR control. Newer drug therapy has become more effective than invasive SN modification with catheter ablation. Future research into IST initiating etiology will undoubtedly improve the long-term success of IST treatment.

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Chapter 41

Ablation of nodal and atrioventricular accessory pathways

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Introduction

0.1%−0.3% of the general population have electrocardiographic findings of a manifest accessory pathway (AP) conduction [1]. APs have the potential to conduct in the anterograde direction, retrograde direction, or both, resulting in different supraventricular tachycardias (SVTs). They can also be bystanders and not participate in a tachycardia. Wolff−Parkinson−White (WPW) syndrome encompasses arrhythmias that occur in the setting of an AP. The arrhythmias in WPW syndrome are [1] orthodromic reentrant tachycardia or atrioventricular reentrant tachycardia (AVRT), in which atrioventricular (AV) conduction goes via the normal AV conduction system and ventriculoatrial (VA) conduction over the AP, and [2] atrial fibrillation (AF)/atrial flutter/atrial tachycardia which goes down the AP. Orthodromic reciprocating tachycardia constitutes 90% −95% of SVTs in patients who have an AP. Ventricular preexcitation and AVRT occur more frequently in men than in women [2].

AF conducting down the AP conduction can lead to sudden cardiac death (SCD) in patients, with a 10-year estimated risk ranging from 0.15% to 0.24% [3]. SCD rarely can be the first presentation of patients with undiagnosed WPW. Elevated risk of SCD is associated with a history of symptomatic tachycardia, multiple APs, and the shortest preexcited RR interval of <250 ms during AF (Fig. 41.1B). It is prudent to risk stratify patients with manifest AP for risk of SCD. The following findings of an RR interval <250 ms between 2 preexcited complexes during induced AF; the presence of multiple APs; the ability to induce sustained AVRT; the finding of AVRT precipitating preexcited AF; and an AP refractory period <240 ms are known to be high-risk features [4].

Historically, surgical ablation of the AP has served as definitive therapy for patients with WPW. The year 1983 was a game-changer in invasive electrophysiology as it marked the initiation of catheter "*fulguration*" of APs with a report by Weber and Schmitz [5]. Subsequently, the use of DC shocks was described by Morady and Scheinman to ablate posteroseptal APs [6]. These initial reports resulted in significant innovation in the field of electrophysiology, as catheter ablation emerged as the first-line therapy for WPW syndrome. Catheter-based AP ablation is one of the most challenging but satisfying procedures aimed at a "cure" with relatively few associated complications. In this chapter, we review the ablation techniques in management of these APs.

Key epidemiological features

There has been considerable interest in sex differences in electrocardiographic patterns since the recording of a high fidelity electrocardiogram (ECG). It is evident that females have longer QT intervals, and this may be partly due to hormonal influence [7]. Epidemiological data regarding sex differences with WPW are available; however, the data cannot be generalized as the population sample is not universal. Adult men are twice as likely to have preexcitation compared to women. Males are also more likely to have symptomatic WPW and referred for electrophysiological study. The sex differences hold true even in young asymptomatic patients with preexcitation. Older patients with manifest APs are more likely to be males; however, concealed APs are equally distributed. A report of AP location by age and sex showed that women were more likely to have tricuspid annular APs [8]. There were no significant reported differences in intraprocedural characteristics as far as sex or ethnicity was concerned. The electrophysiological characteristics of the APs are no different in males versus females (Table 41.1) [9].

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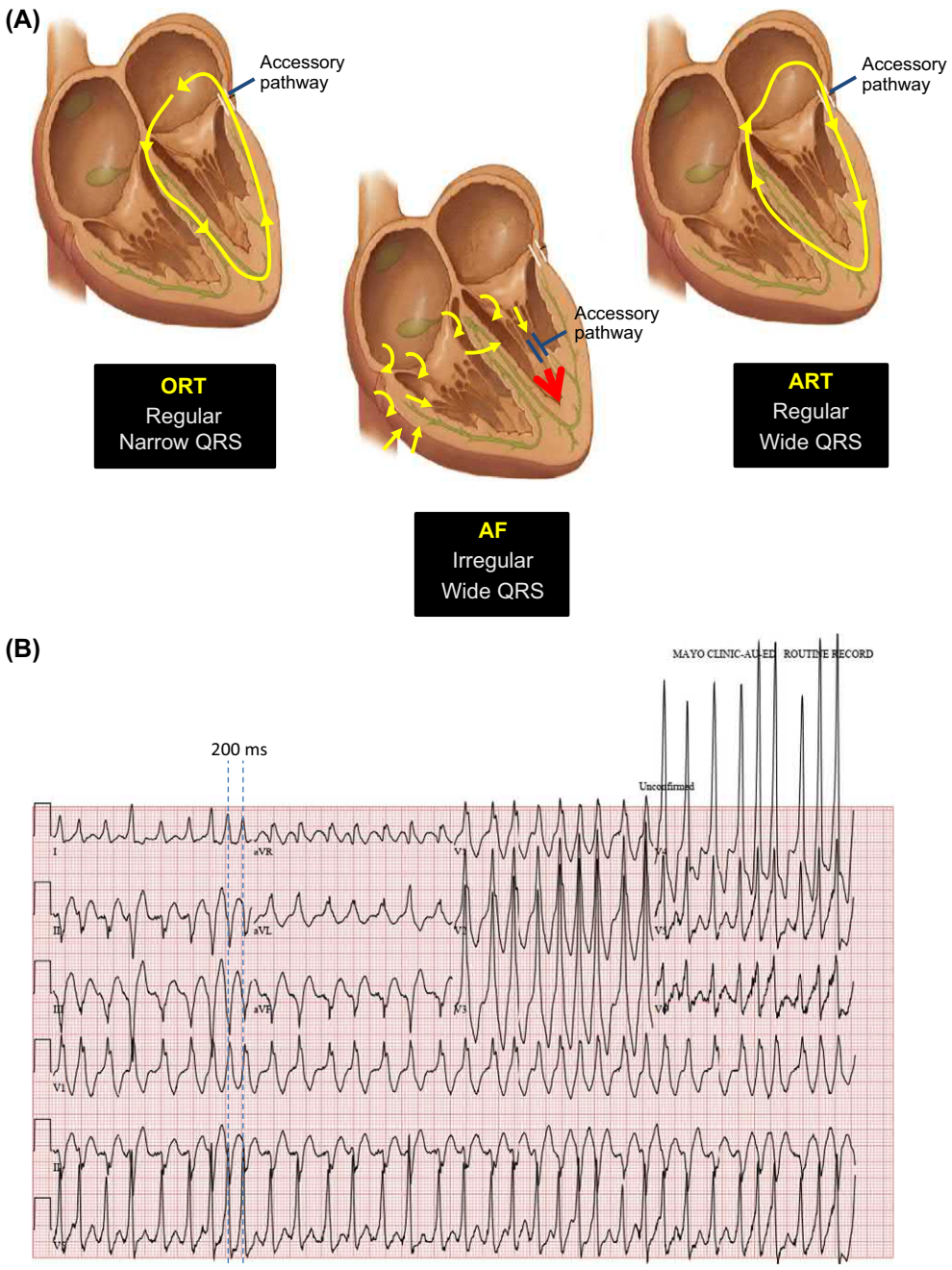

FIGURE 41.1 (A): Accessory pathway–related arrhythmias. (B): 31-year-old male with preexcited atrial fibrillation. Note the shortest RR interval of 200 ms conferring a high risk of sudden cardiac death.

Ablation principles for atrioventricular pathways

Ablation of free wall pathways

Anatomical considerations

A century ago, Tawara made the path-breaking discovery that a solitary myocardial pathway provided conduction between the atrial and ventricular muscle [10]. The atria are physically and electrically disconnected from the ventricles by fibrous tissue [11]. The genesis of the annulus fibrosus is dependant on the integration and fusion of sulcus tissue during early atrial and ventricular folding. This results in the electrical and structural insulation between the atrium and ventricle. The His bundle is the only true electrical connection between the atria and the ventricles. Any breach in this insulation on the AV annulus results in another path through which the atrial and ventricular mass is electrically

TABLE 41.1 Proportion of accessory pathways (APs) in males and females in each location.

AP location	AP in males (n = 185) (%)	AP in females (n = 115) (%)
Left posterior	87 (47)	42 (37)
Right inferoparaseptal	18 (10)	26 (23)
Left inferoparaseptal	25 (14)	3 (3)
Right anterior	20 (11)	19 (17)
Right septal	3 (2)	6 (5)
Right superoparaseptal	11 (6)	10 (9)
Right inferior	6 (3)	3 (3)
Left inferior	11 (6)	4 (3)
Right superior	2 (1)	1 (1)
Left superior	2 (1)	1 (1)

Overall chi-square p-value = 0.003.
Adapted from Hsu JC et al. Hsu JC, Tanel RE, Lee BK, Scheinman MM, Badhwar N, Lee RJ, Tseng ZH, Olgin JE, Marcus GM. Differences in accessory pathway location by sex and race.Heart Rhythm. 2010; 7:52–56. doi: 10.1016/j.hrthm.2009.09.023

connected. These are referred to as the APs and are epicardial to the valve annulus. These abnormal connections traverse the insulating annulus at the AV junctions, and they can be found at any point in the cardiac development where the atrial myocardium is in communication with the underlying ventricular myocardium. The presence of these connections results in ventricular preexcitation through early activation of the ventricle *bypassing* the His bundle and provides a potential fast or a slow zone for reentrant tachycardias [12]. The variants of APs linked to the actual AV conduction system, such as fasciculoventricular or nodofascicular tracts, are due to failure of transcription factors NKX2-5 during His bundle and right bundle development [13].

The mitral annulus (MA) is formed by the left atrium, the left ventricle (LV), and the mitral leaflets. It resembles a kidney bean [14]. The histologic descriptions of left free wall APs by Becker have elucidated that the atrial connection is usually discrete and near the annulus (Fig. 41.2B) [15,16].

The ventricular insertion can be discrete or multiple connections with the ventricle that may be displaced away from the annulus. The length of an AP is typically 5–10 mm. The epicardial aspect of the MA comprises of the left circumflex artery near the annulus and the coronary sinus (CS) more distant and posterior from the annulus. The anterior boundary of the left free wall is defined by the aorto–mitral valve continuity, which rarely contains AP connections (lost connections). This is intuitive as there is no real atrial and ventricular communication on the aorto–mitral continuity. The posterior limit is continuous with the posteroseptal area. Although the CS is useful for quick surrogate mapping of the MA, it is located 1–1.5 cm posterior to true annulus. This separation from the annulus is more noteworthy in the proximal 2 cm of the CS. This understanding is paramount for accurate mapping of the annulus and not inferring annular signals based on the electrograms from the multielectrode catheter in the CS. However, a ballpark location of the potential pathway can be deduced based on the activation sequence noted on the multielectrode mapping catheter in the CS, and further mapping on the true annulus can be performed to identify the pathway potential.

The anatomy of the tricuspid annulus is more challenging from a mapping perspective [17]. The tricuspid annulus has an elliptical saddle shape. The posteroseptal boundary (close to the CS) and the anterolateral boundary are the closest to the apex, and the anteroseptal (close to the RV outflow tract and the aortic valve) and posterolateral edges are adjacent to the right atrium. The tricuspid valve annulus is less well formed and is frequently interrupted compared to the MA. The right atrial and right ventricular myocardia fold over one another as they insert on the tricuspid annulus. As compared to the left side, there is rarely a multielectrode catheter placed along the tricuspid annulus to give additional data. Even if a catheter is placed, it is not able to span the entire tricuspid annulus due to its elliptical saddle shape. The acute angulation of the tricuspid

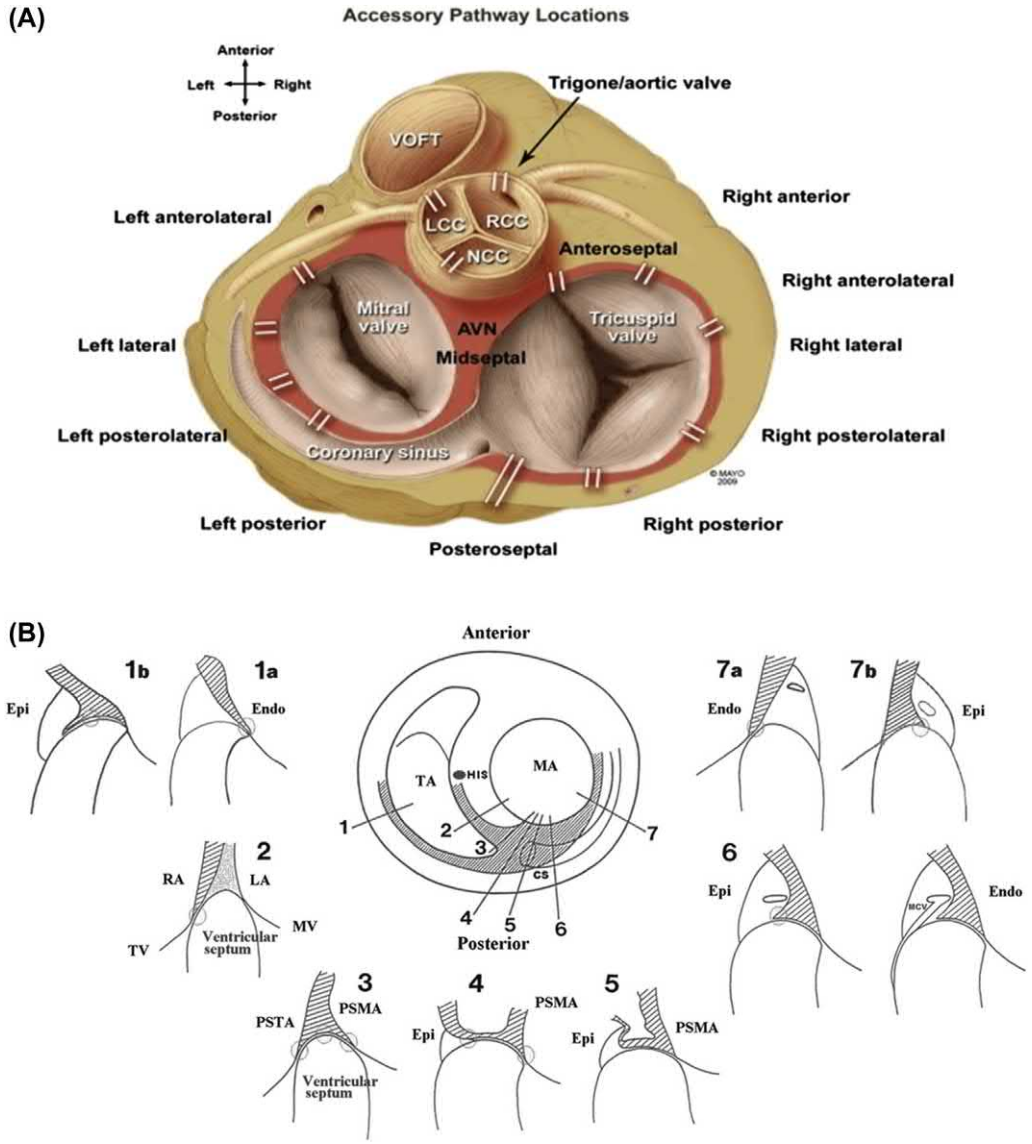

FIGURE 41.2 (A): Atrial ventricular accessory pathways may occur anywhere along the atrial ventricular annulus. Note the posteroseptal region is not a part of the true septum. Note also the position of the aortic annulus interspersed between the right and left anteroseptal regions. (B): Anatomy at the level of AV annuli. *Red circles* depict possible APs in sagittal Sections 1−7. Shaded area depicts atrial myocardium. 1: Right free wall; 2: Midseptal region; 3: Posteroseptal tricuspid or mitral annulus; 4 and 5: Coronary sinus ostium and adjacent structures; 6: Left posterior wall or middle cardiac vein (MCV); and 7: Left free wall. *Adapted from Liu et al.*

leaflets toward the ventricle makes catheter positions along the right free wall challenging. Hence, mapping along the tricuspid annulus is more arduous as compared to the MA.

Mapping principles

Accurate placement of mapping catheters is crucial for a thorough assessment of AV and VA conduction. No pathway case should be performed without the placement of a multielectrode catheter across the His bundle location and catheter in the CS advanced as distally as possible along with catheters in atrium and ventricle for stimulation.

Mapping and ablation for the left free wall pathways may be performed by the retrograde approach or the transseptal approach. Most modern-day electrophysiologists utilize a transseptal approach. Using the retrograde approach, the catheter tip is directed at putative locations below the MA to target the ventricular insertion of the AP. The catheter is always prolapsed across the aortic valve using either the small or the larger curve to prevent perforation of the leaflets or inadvertent coronary artery cannulation. The initial curve to cross the aortic valve is dependant on the size of the aortic root and tortuosity. The catheter is then torqued in a counterclockwise direction to

turn the tip more posteriorly toward the annulus. The catheter tip can get stuck in the papillary muscles or the chordae tendineae; hence, the tip has to be free. It is often challenging to achieve stable catheter positions for the far lateral and anterior MA with the retrograde approach. It is also likely that the catheter pulls back into the aorta; hence, multiple attempts may be needed to cross the aortic valve. The transseptal method aids in mapping the atrial side of the annulus or the MA itself. The transseptal puncture can also be planned based on the electrocardiographic location of the pathway [18], and a steerable sheath or SL1, SL2, or SL3 sheath can be used. The use of intracardiac echocardiography also helps in assessing catheter contact and assessing unusual variants such as pouches or ridges.

Mapping the tricuspid annulus is more challenging due to its unique anatomical orientation, as described above. Multielectrode catheter spanning the tricuspid annulus can be considered. However, it should be noted that it is not going to span the entire annulus due to the acute angulation of the tricuspid leaflets toward the ventricle. Use of multielectrode catheters, or rarely, 2.3 French mapping catheters positioned in the right coronary artery represent the closest surrogates to CS mapping for the right side of the heart [19] (Figs. 41.3 and 41.4B). However, point-by-point mapping carefully looking at the atrial and ventricular signals can suffice majority of the time. Catheter mapping from the subclavian vein or right internal jugular vein approach is sometimes more favorable than the femoral approach to get the catheter tucked underneath the annulus.

A systematic method of mapping the annulus by noting the septal, lateral, anterior, and posterior aspects of the annulus needs to be acquired. Unique challenges of contact, respiratory motion, and the presence of other catheters in the right atrium can make overall mapping cumbersome. Also, the placement of catheters too close to the location of the pathway can result in mechanical trauma or "bump" the pathway; hence, the operator has to be mindful of this possibility.

Electrograms

The success and failure during pathway ablation are dependent on accurate interpretation of electrograms and not having a "burn and see" response. Stable catheter position is confirmed fluoroscopically or via mapping systems. Assessing contact force and observing a stable electrogram is critical. Generally, the local ventricular electrogram on the mapping catheter should precede the onset of the delta wave on the ECG by a mean of 0−10 ms for left-sided APs and 10−30 ms for right-sided APs

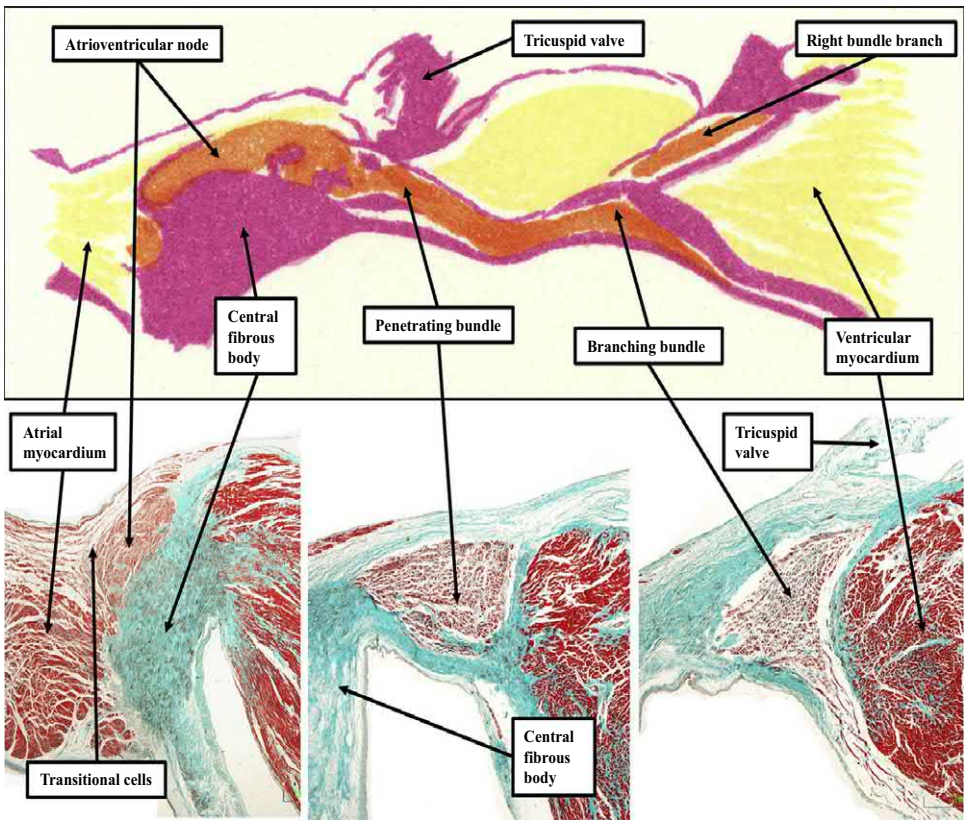

FIGURE 41.3 Tawara's description of the AV conduction system. *Adapted from Anderson RH et al.*

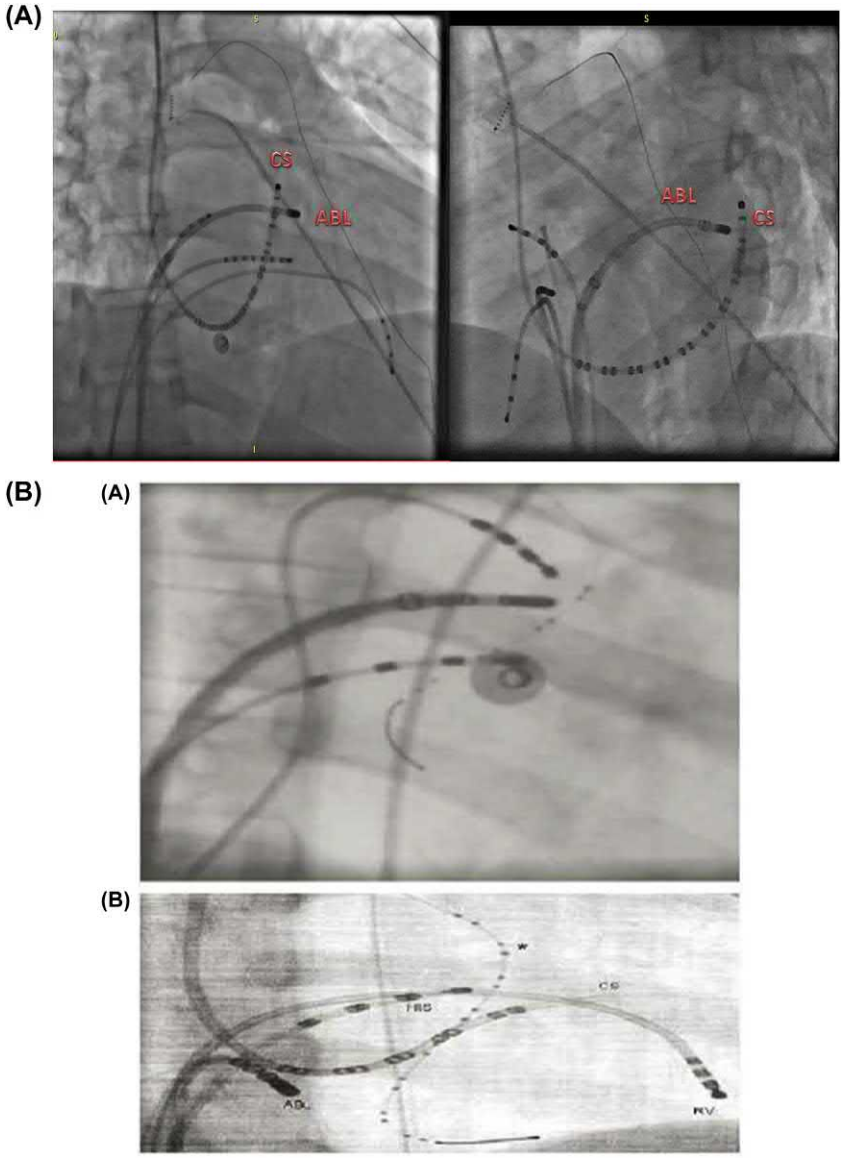

FIGURE 41.4 (A): Catheter positions in a successful left lateral pathway ablation. *ABL*, ablation catheter; *CS*, coronary sinus catheter. (B): 2.3 Fr. RCA catheter used to map right-sided accessory pathway. *Dubin AM. Right-Sided Accessory Pathways | Thoracic Key. doi:8/27/2018.*

(Fig. 41.5) [5]. The local ventricular electrogram is measured from the first near field peak of the bipolar electrogram or the maximal dV/dt in the unipolar electrogram. Right-sided APs usually have unipolar recordings that show more pronounced (rapid and deeper) QS configuration than left-sided APs. Local VA interval during retrograde activation of the AP can seldom be short. However, a short VA does not mean the site of ablation. Long VA intervals can be noted in previously damaged, slowly conducting, oblique, or epicardial APs. It is also dependant on the site of ventricular pacing. The local VA interval should remain fixed regardless of the direction in which the ventricular wavefront engaging the AP is traveling, despite pacing from different ventricular sites. The ventricular insertion site can be identified as one that has a fixed local VA interval, despite changing the pacing wavefront to the site. All these methods have certain nuances and limitations which have been described subsequently.

As the entire premise of successful AP ablation is the AP ablation, the critical electrogram which has to be teased out is truly an AP potential.

The accessory pathway potential

The fusion of the atrial and ventricular electrograms, the earliest ventricular electrogram during atrial pacing, the earliest atrial electrogram during ventricular pacing (with

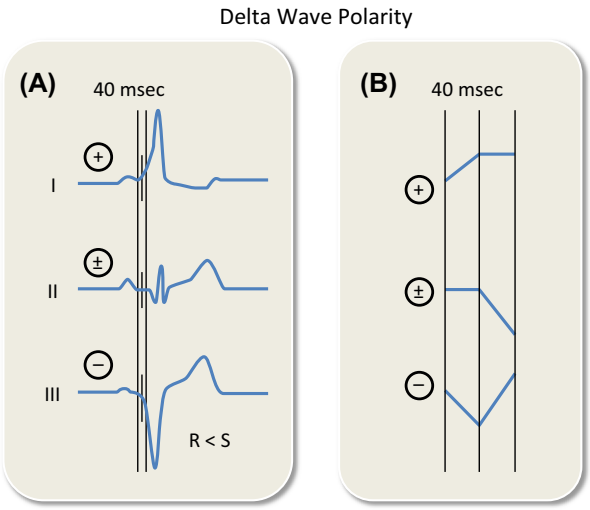

FIGURE 41.5 Delta wave polarity was determined by examining the initial 20 msec after earliest delta wave onset in the limb leads as well as precordial leads. (A) ECG leads I, II, and III of a patient with an accessory pathway located at the posteroseptal tricuspid annulus region. Note that it is possible to determine delta wave polarity in all three leads at approximately 20 ms after the onset of delta wave. (B) Determination of delta wave polarity (using the initial 20 ms) in the event of changes within 40 ms.

retrograde conduction), and identification of the pathway potential are some of the methods described for a successful AP ablation. The pathway can be ablated by any of these methods; however, these methods are fraught with assumption that the APs are vertical rather than slanted.

The most natural and easiest site to find but the poorest choice for ablation is the fusion of the atrial and ventricular electrograms. It is noteworthy that even in the absence of AP, AV fusion is noted due to concurrent activation of atrial and ventricular myocardium on the annulus (pseudointerval). While assessing electrograms on a multielectrode catheter placed in the CS, AV fusion is frequently seen. This is seen despite no AP conduction. There is no conduction between the atrium and ventricle from the CS unless there is a pathway. Understanding and practicing the techniques to map the AP potential remains the most precise method for pathway ablation. Analyzing complex signals can be challenging; hence, an approach of association of and dissociation of the signals needs to be undertaken to decipher each signal and target the AP potential [20].

During atrial pacing, if a potential is noted between the atrial and ventricular electrograms during preexcitation, one must try to infer whether the signal is atrial, ventricular, a His bundle recording (in certain situations), or represents the true AP potential. Simple and straightforward maneuvers can be performed to infer the potential of interest.

(1) When the atrium is paced to AV block and the potential is still present, as there is no ventricular activation, hence the potential of interest is not a ventricular electrogram. It can still be an atrial signal or AP potential.
(2) If with ventricular pacing, VA block is noted and the potential of interest is absent, then it cannot be an atrial signal.
(3) If the potential of interest is not altered despite advancing the ventricular electrogram by placing sensed PVCs, then the potential of interest has also been dissociated from the ventricle.

If the potential of interest has been dissociated from the atrium and the ventricle, an AP potential can be inferred (Fig. 41.6).

The AP potential manifests as a sharp near field signal on both unipolar and bipolar recordings generally 10–30 ms before the onset of the delta wave during preexcitation or between the ventricular and atrial electrograms at the earliest site of retrograde atrial activation during orthodromic AVRT or ventricular pacing. Targeting an AP potential has been associated with the highest rate of ablation success (Fig. 41.7). However, the difficulty in identifying the AP potential is often related to the oblique or slanted course of the BT and, more importantly, inertia from the operator to spend the time to account for each signal.

The pathway slant

APs are not oriented vertically to the mitral or tricuspid annulus. The multielectrode mapping catheter in the CS is parallel to the MA. The AV interval and the VA interval occur when pacing on either side of the AP. If there is a change in the VA or AV interval with the change in pacing site, then the presence of a slanted AP can be inferred [20]. When an antegrade conducting pathway has its atrial insertion septal to its ventricular insertion at the pathway site, the CS electrode will record an atrial electrogram while pathway conduction is already occurring (along the slant) resulting in a short AV interval. When pacing from a lateral location, the atrial electrogram will be inscribed first even before the atrial insertion of the pathway has been activated, thus giving rise to a long AV interval. This becomes important while mapping the pathways and optimizing the site for ablation (Fig. 41.8).

Mapping for an AP potential with the wavefront against the slant (long AV interval) maximizes the chance of seeing the pathway potential. Due to the presence of a long AV interval, there is more chance of seeing an AP potential. Each signal can be further interpreted by the associative and dissociative maneuvers, as described above. Appreciating

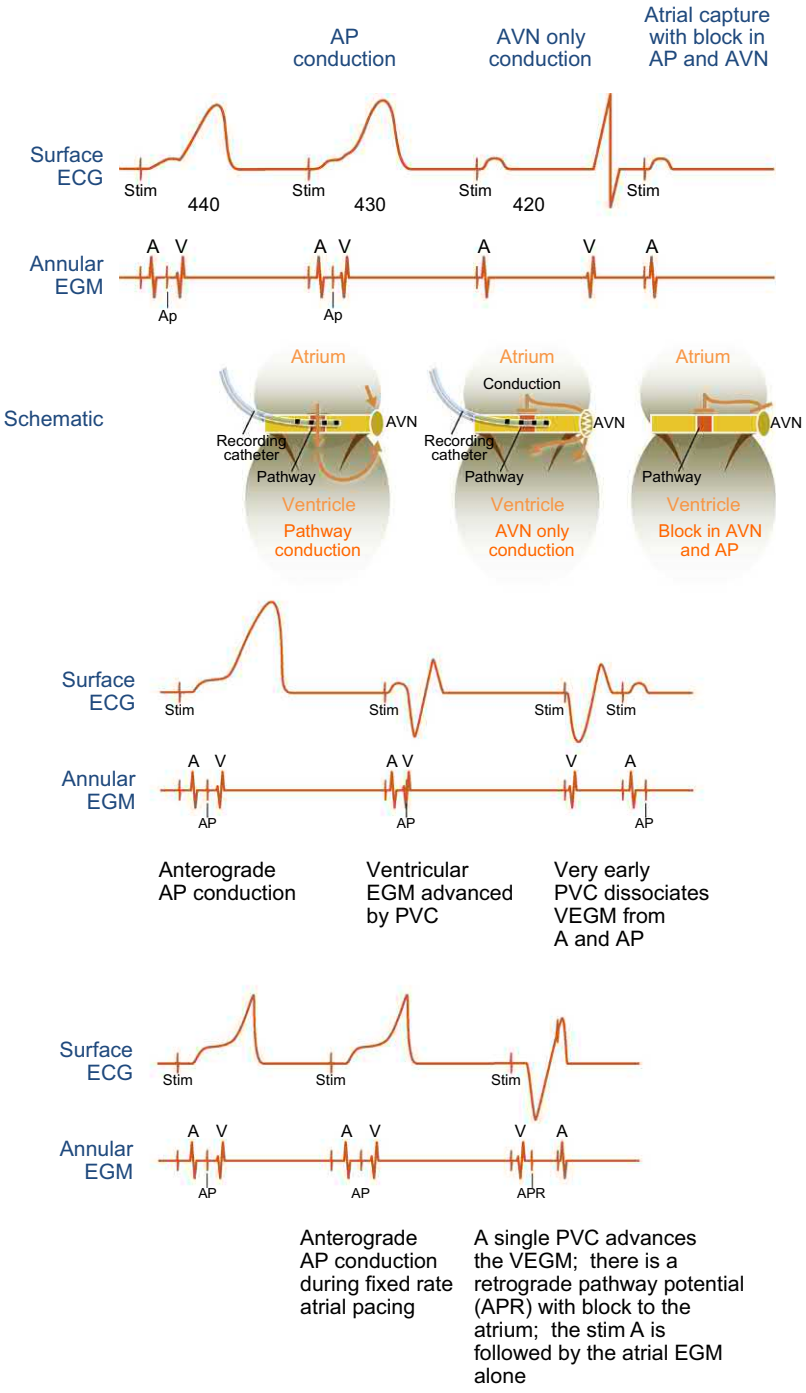

FIGURE 41.6 Associative and dissociative maneuvers.

the actual direction of the slant may help to target the ventricular insertion if that insertion is further away from a critical structure such as AV node.

Ablation: The ablation can be performed during normal sinus rhythm or, preferably, atrial pacing in patients with manifest AP. The ablation is performed during ventricular pacing in patients with concealed AP as it allows for evaluating a change in retrograde atrial activation sequence. RF energy delivery during tachycardia is avoided due to movement of the catheter after the tachycardia is terminated [21]. This can lead to partial damage to the pathway without resulting in permanent damage to the AP due to premature interruption of the RF application. Ablation during continuous pacing prevents this problem.

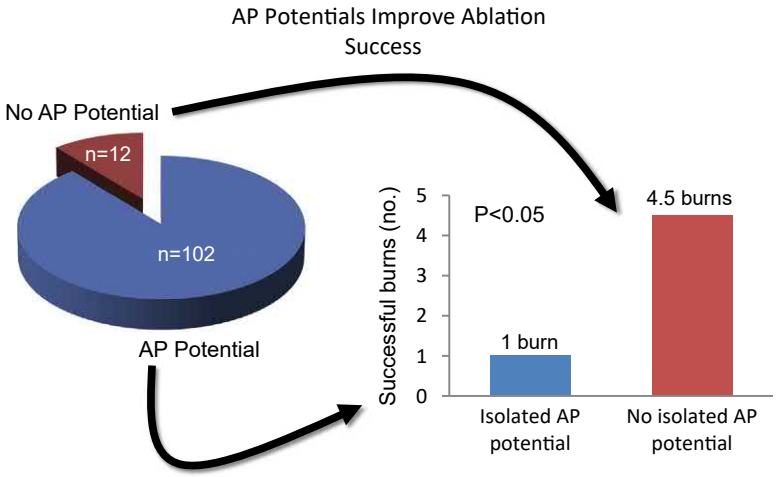

FIGURE 41.7 Ablating AP potential versus no isolated AP potential. *Otomo, Jackman, et al. Circulation 2001:104; 550–556.*

A complete bidirectional block can be achieved with a 5-mm-tip nonirrigated ablation catheter, using a power setting of 50 W and targeting a temperature of 60°C. Block in the AP can be achieved with good and consistent contact at the site of AP potential. The failure of AP ablation once accurate mapping of the AP potential is performed is almost due to poor tissue contact and not the inadequacy of the lesion size [22]. In current times irrigated bidirectional catheters along with contact force may also add an additional dimension for assessing contact and help in ablation. Loss of BT conduction is expected within 1–6 s of RF application (once the target temperature and power delivery have been reached) for most successful lesions (Fig. 41.9). If no effect is seen, the RF energy delivery should be stopped as it is likely to create edema formation which may prevent further energy delivery [23].

The ablation for right-sided APs is more challenging than that of left sides APs due to anatomical orientation of tricuspid annulus and lack of multielectrode mapping catheter spanning the entire tricuspid annulus [24]. The recurrence rates over the first few weeks after initially successful AP ablation are more common with right-sided pathways compared with left-sided pathways. The folded-over atrium and the acute angle for mapping of the inferior and posterolateral aspect of the RA by a catheter passed through the inferior vena cava (IVC) can make it difficult to achieve a stable catheter position at the tricuspid annulus because of a tendency of the catheter to fall more atrially. Seldom the superior vena cava approach is required to allow complete mapping of the inferior–inferolateral positions around the tricuspid annulus (Fig. 41.10). The standard IVC approach is ideal to map the superior and anterior aspects of the tricuspid annulus. This is also facilitated with a steerable sheath for better tissue contact.

Ablation endpoint

Loss of bidirectional AP conduction is the endpoint for a pathway case. Lack of inducibility is expected once the AP is ablated; however, lack of inducibility of SVT in presence of a partially damaged pathway should not be the endpoint. Confirmation of loss of anterograde AP conduction properties using atrial decremental pacing and atrial extrastimulus testing is achieved by demonstrating lack of preexcitation and marked prolongation of the local AV interval at the ablation site. Atrial pacing should be performed at sites adjacent to the pathway location. Similarly, ventricular pacing should be performed at sites adjacent to the pathway location (LV pacing for LV free wall pathway).

Septal accessory pathways

General principles

Septal APs are challenging to ablate compared to free wall APs. The potential reasons include precise mapping, interpretation of electrograms, and risk of AV block. Hence, it is important to understand the anatomy and practical yet nuanced methods for electrogram interpretation and targets for ablations. It is noteworthy that the septal APs are associated with a higher recurrence rate and risk of AV block with ablation [25]. The septum is divided into anterior and posterior divisions. The anterior boundary is constituted by the tricuspid and the MA, the aortic annulus, the membranous ventricular septum, and atrial septum, i.e., the right fibrous trigone. The posterior boundary of the septum is formed by the posteromedial aspects of the left and right atrium, the posterior confluences of the left and right ventricular walls, and the epicardium over the crux of

the heart. The operator should be aware that the AV node is housed in the triangle of Koch. The boundaries of the triangle are made by the tendon of Todaro (linear tissue that runs from the central fibrous body to the Eustachian ridge) posteriorly, the tricuspid annulus anteriorly, and the CS ostium septally. The septal APs occur circumferentially along the annuli of the mitral and tricuspid valves [16,26].

Mapping principles

Some of the techniques described earlier and subsequently are paramount for an accurate deciphering of the signal of interest (pathway potential) for ablation. However, it is even more imperative to understand it, especially in the septal region due to the risk of AV block and higher risk of recurrence [25].

Pseudointerval: A pseudointerval is an interval between two potentials that is caused by activation of a common site that propagates to activate sites that are responsible for each of the potentials. It does not result from conduction between the site responsible for the first potential to the site responsible for the other potential. Therefore, the local VA or the AV interval, when recorded through a multielectrode placed along the annulus (CS catheter) does not represent the actual conduction time through A to the V or V to the A in that location [25].

Fused electrograms (AV or VA): The ablation trigger response to ablate shortest AV (atrial pacing) or VA interval (ventricular pacing) should be withheld (fused AV or VA signals). Depending on the pacing site, the VA interval maybe 0 ms at sites far away from the actual AP. In those instances, the short interval is simply a reflection of simultaneous activation of the atrium and ventricle at that time (pseudointerval) picked up by the electrode on the annulus. This can be potentially sorted out by pacing close to the AP site.

Earliest electrogram: Although this technique can be applied here again on the septum, it is not ideal. For example, the earliest atrial activation for a downward slanted posteroseptal pathway may be very close to the compact AV node, and safe ablation could have been done more ventricular on the annulus itself to avoid the risk of AV block [27].

The pathway potential: In general, mapping and ablating the AP potential is the most robust method to achieve success. Dissociative and associative pacing maneuvers are performed to tease out each of the electrograms. Once AP potential is confirmed and, more importantly, AV node sites (far-field His signals in the triangle of Koch), the pathway potential can be targeted for energy delivery.

Pathway slant: One manifestation of pathway slant is an anatomic separation in the site of the earliest ventricular and earliest atrial activation in pathways that exhibit bidirectional conduction. Thus, a bipolar mapping electrode placed on the annulus at one site may find the site of earliest activation but may need to be advanced further along the annulus to locate the site of earliest ventricular activation

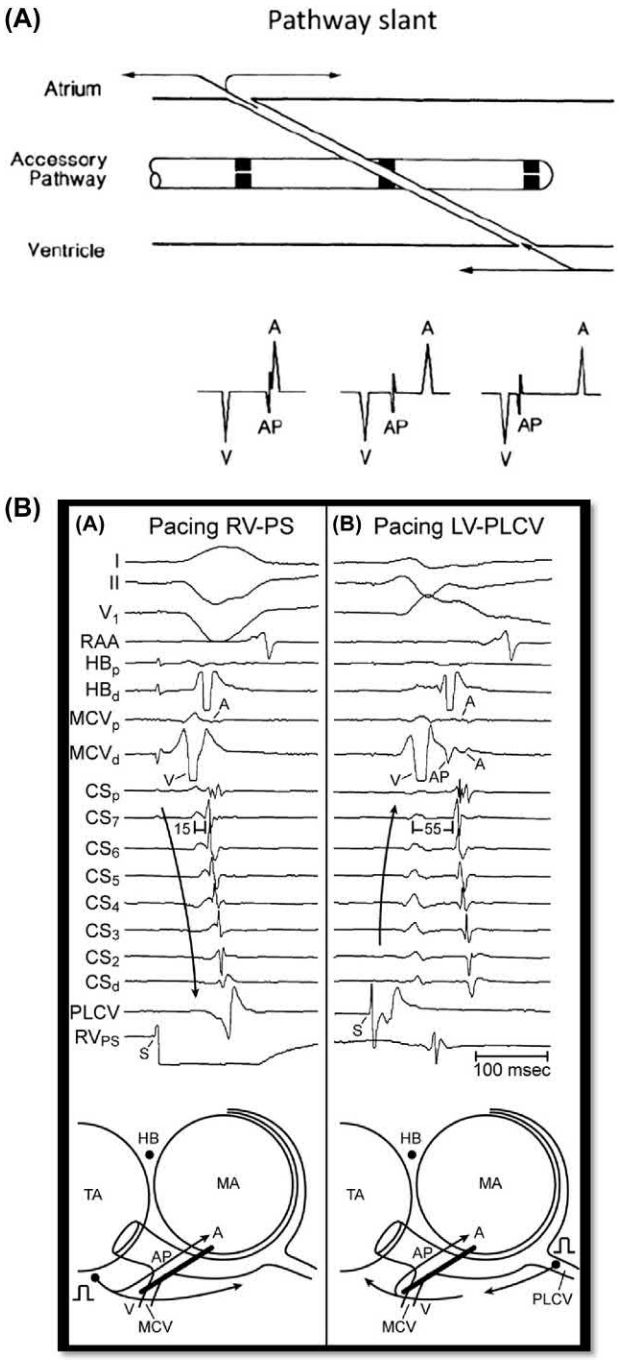

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FIGURE 41.8 (A): Demonstration of slant. (B): Changing ventricular pacing site changes the local VA interval suggesting slanted pathway. (C): Once change in local VA interval is noted, slant is conformed. Pacing is performed to see AP potential during the longest local VA interval. *Otomo, Jackman et al. Circulation. 2001:104; 550–556.*

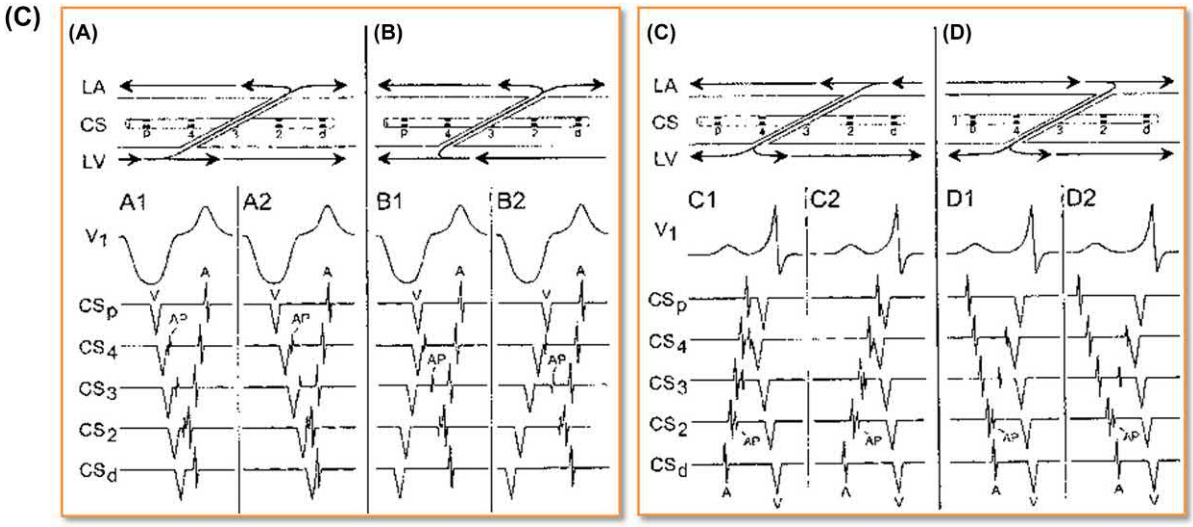

FIGURE 41.8 cont'd

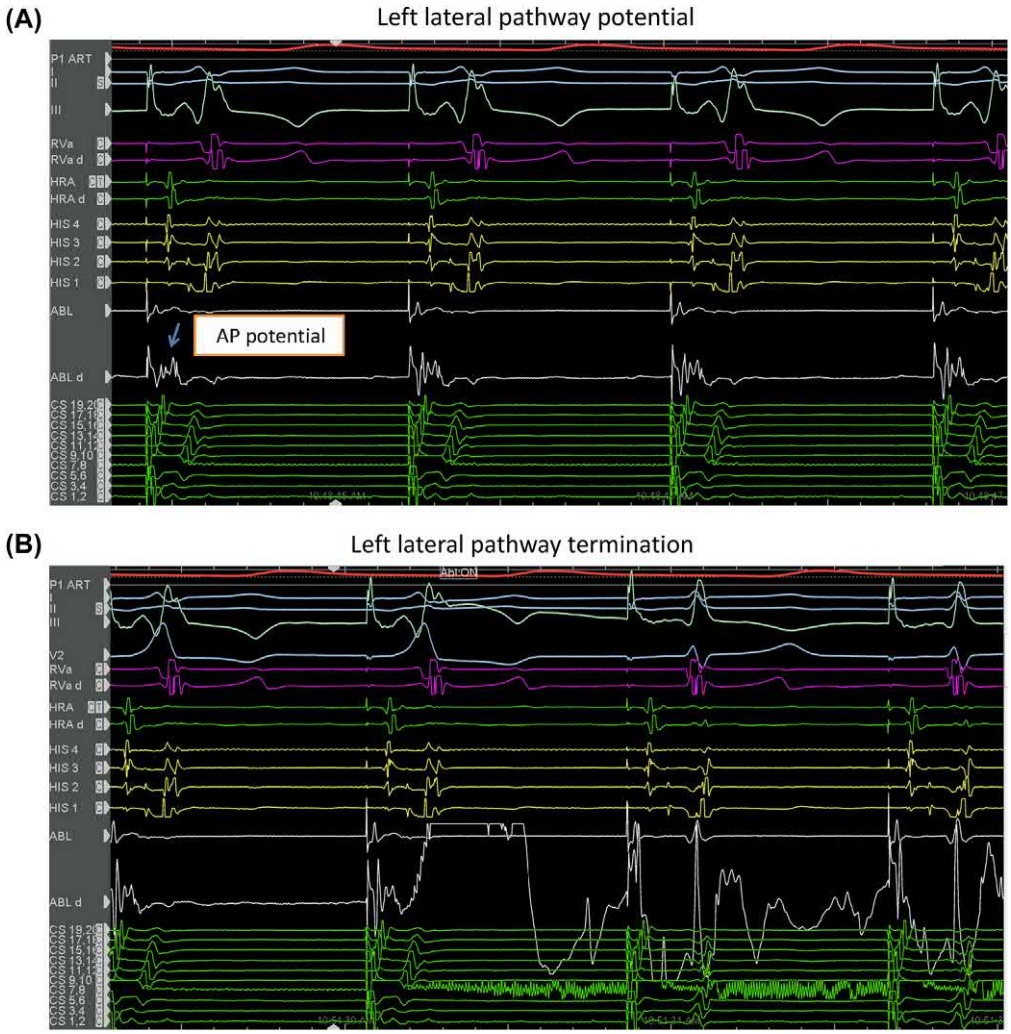

FIGURE 41.9 (A): Accessory pathway potential. (B): Loss of accessory pathway conduction during ablation.

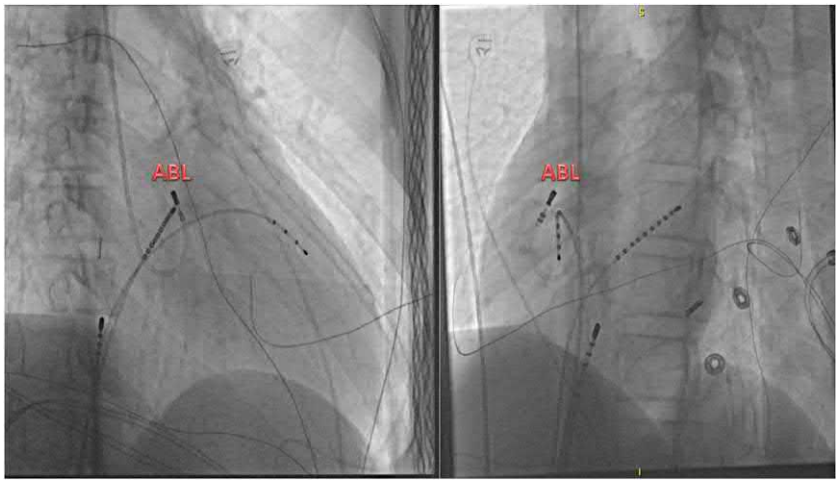

FIGURE 41.10 Superior vena cava approach to map and ablate right-sided accessory pathway.

during sinus rhythm or atrial pacing. Unlike the free wall pathways, the septal pathways slant from superior to inferior direction [25]. Thus, the superoinferior slant in the septum can be evaluated by pacing superior to and inferior to the insertion site of the pathway. Thus, the presence of a closely spaced multielectrode catheter noting the His bundle signals is crucial. If this construct of the slant is clear, then the target can be chosen to ablate along the slant in such a way as to avoid potential collateral damage.

Ablation

Generally, a right-sided femoral venous approach is chosen for mapping and ablation of APs in the posteroseptal region. The posteroseptal tricuspid annulus, including the CS os and its most proximal part, and inferomedial right atrium are carefully mapped. If the ablation site fails or no appropriate ablation site can be obtained, the left posteroseptal area is mapped with a transeptal approach. The use of steerable sheath is crucial to map in this location. A standard SL2 or SL3 sheath will take the catheter away from the septum. If endocardial mapping does not show any potential sites, then mapping the CS is considered.

Although a nonirrigated catheter could be reasonable to ablate pathways in general, an irrigated catheter is a reasonable choice for a posteroseptal AP. When ablation is being performed in the middle cardiac vein for a true epicardial pathway, coronary angiogram is important to assess the distance from the posterolateral branch of the right coronary artery. Notably, a coronary branch was usually within 2 mm of the ablation site (59%), reasonably close (3−5 mm) in 16%, and safely away (>5 mm) in 25% while ablating epicardial posteroseptal pathways [25,26].

Besides, the impedance will be higher in the middle cardiac vein if the catheter is too deep-seated or wedged. For irrigated RF in the CS, a starting power of 5−10 W and uptitration based on impedance and effect is reasonable. Sometimes the impedance cutoff may need to be increased to prevent premature termination of ablation. Besides, manually increasing irrigation flow or considering half normal saline may prove efficacious. The ablation of posteroseptal APs is associated with higher success rates (up to 98%) and a recurrence rate of 12%. The ablation of epicardial APs (within the CS) is associated with a success rate of 62%−100% and a complication rate of 0%−6% [28].

Midseptal pathways

General principles

The midseptal pathways account for 5% or less of all APs in most series. The majority of midseptal APs show anterograde conduction (15% are retrograde only), with only about 4% conducting anterograde only.

The compact AV node resides in the midseptum. The electrophysiologist must be cognizant of the triangle of Koch anatomy and, more importantly, the fact that the AV node is an atrial structure. Thus, for a true midseptal pathway, care should be performed not to target the atrial insertion of midseptal pathways due to likelihood of ablating the AV node. The tricuspid annulus is located relatively more caudal to the MA, a unique portion of the cardiac septum exists not part of either the interatrial or the interventricular septum [17]. This AV septum separates the right atrium and the LV with septal tissue that is composed primarily of LV myocardium with contribution from right ventricular myocardium and the right atrium. Thus, it is

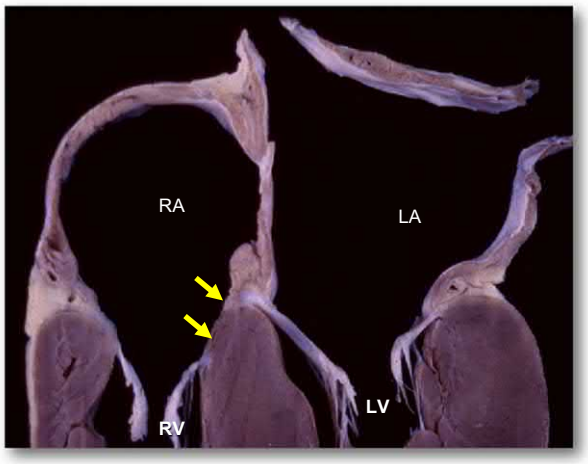

FIGURE 41.11 This figure illustrates the caudal location of the tricuspid annulus compared to the mitral annulus and potential sites to map the atrioventricular septum both from RV and LV.

evident for the APs to have their atrial insertion in one atrium and the ventricular insertion in the contralateral ventricle (Fig. 41.11).

Ablation

Second- and third-degree AV block has been reported especially in children undergoing septal AP ablation [29]. In the Pediatric Radiofrequency Ablation Registry as expected, the ablation of midseptal APs was more frequently associated with accidental AV block (10.4%) in comparison to other septal locations (anteroseptal 2.7% and posteroseptal 1%) [30].

Hence, as described in earlier sections, assessing a true AP potential for ablation, not ablating the earliest A (most important for midseptal pathways), clear interpretation of signals, can facilitate successful ablation. RF energy should never be applied as first-line therapy in the midseptal region and attempts with cryoablation first are generally prudent.

Cryomapping should be performed whenever possible to check whether ablation at the site of interest will have the desired effect (i.e., block in the AP) and without the risk of AV block. Cryomapping is performed at −30°C at the location of interest. At this temperature, the lesion is reversible (for up to 60 s), and the catheter is "stuck" to the endocardium in an ice ball that includes the tip of the catheter (cryoadherence). During this time pacing maneuvers can be performed to test for AP conduction. In the cryomapping mode, the temperature is not allowed to drop below −30°C, and the time of application is limited to 60 s [31].

When sites of successful cryomapping are identified by demonstrating AP conduction block with no modification of the normal AV node conduction, the cryoablation is performed, in which a target temperature below about −75°C is sought (a temperature of −75 to −80°C is generally achieved). The application is then continued for up to 480 s, creating an irreversible lesion. However, pacing needs to be continued to look for a change in AV node properties. If the catheter tip is in close contact with the endocardium, a prompt drop in catheter tip temperature should be seen as soon as the cryoablation mode is activated. A slow decline in temperature or very high flow rates of refrigerant during ablation suggests poor catheter tip−tissue contact and, in such a case, cryoablation is interrupted and the catheter is repositioned. Additional cryoablation applications (freeze−thaw−freeze cycles) may be applied as insurance lesions [32].

If, however, RF energy is being considered, RF delivery should be immediately discontinued when there is any PR prolongation or junctional rhythms before things are reassessed. Finally, there has to be a clear discussion with the patient and the family of the need for pacemaker before any energy delivery.

Anteroseptal pathways

Anteroseptal APs comprise 6%−7% of all APs. About 80% of these APs exhibit anterograde conduction, and 20% are retrograde-only conducting (concealed); only about 5% conduct exclusively in the anterograde direction [23,25]. The bundle of His is a well-insulated structure and is covered with fibrous annular tissue. This insulation is lost as the His bundle continues as the right bundle exits to the myocardium. Hence, ablation is reasonably safer on the His bundle itself compared to the compact AV node. It is important not to ablate on the atrial side of the annulus and not to allow the catheter to drift lower onto the midseptum where the compact AV node is located. As with midseptal pathways, it is generally preferable to attempt ablation with cryo energy after the pathway has been mapped in this region.

There are situations in which an anteroseptal AP could be ablated from the noncoronary aortic cusp [33] (Fig. 41.12). The ECG clue for this is a presence of a small R wave in lead v1. This suggests the pathway is somewhat off the septum. The aortic sinus of Valsalva and the aortic annulus separate the two atria anteriorly. Myocardium potentials have been encountered in the supravalvar area. These myocardial tissues traverse the aortic valve connecting the atrial and ventricular myocardium could

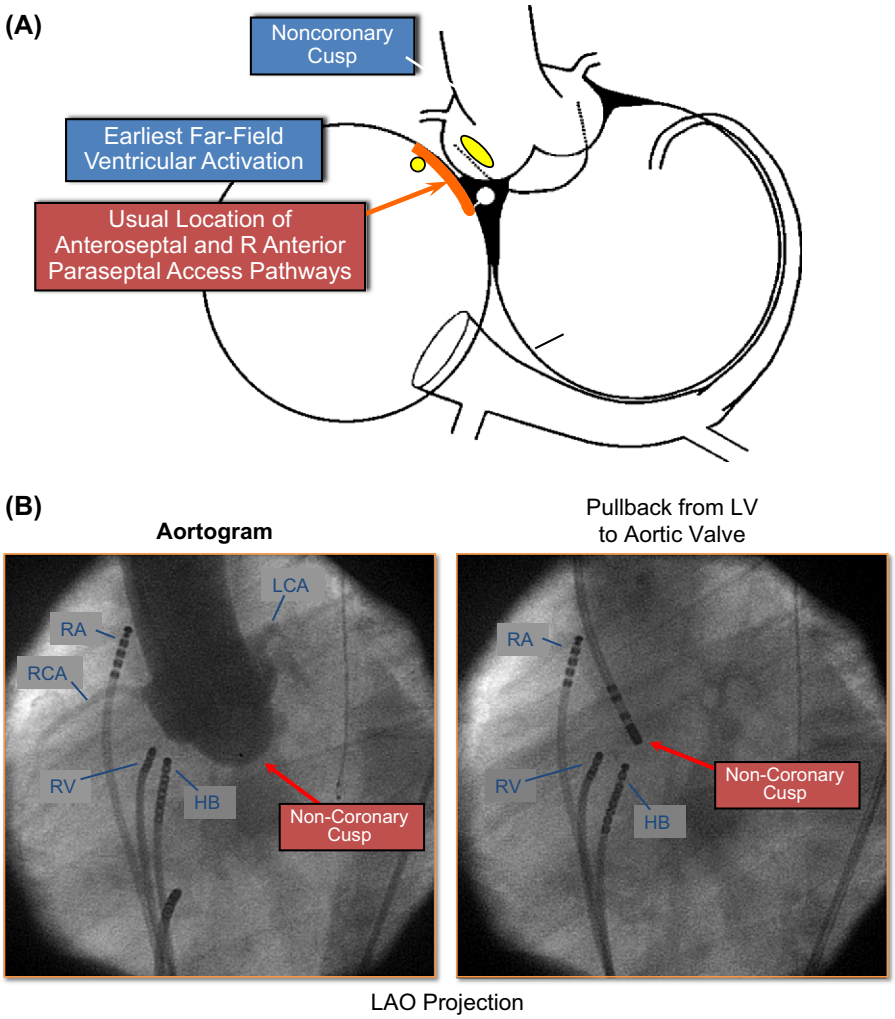

FIGURE 41.12 (A): Schematic for anteroseptal and right anterior paraseptal accessory AV pathways and relationship with noncoronary cusp. (B): Fluoroscopy in LAO view showing relationship between catheter at His bundle location and noncoronary cusp.

constitute the AV connection (AP). Another possibility is that they transverse the fibrous trigone in this region of the heart. In this context, it is very important to remember mapping the aortic valve region as another vantage point whenever mapping for an anteroseptal pathway.

Conclusion

Since the pioneering work in the 1980s, catheter ablation of APs has emerged as a safe and effective tool in our armamentarium against WPW syndrome. We urge the electrophysiologist to be vigilant in identifying the role of APs in arrhythmias, and once identified, use the principles outlined in this chapter to successfully perform ablations. Anatomic principles pertaining to specific pathways must be utilized in each and every case. Key concepts to remember are the importance of mapping pathway potentials and recognizing the reasons for the failure of ablations.

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Part XI

Atrial fibrillation

Chapter 42

Rate control of atrial fibrillation

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Rate control is a fundamental treatment strategy in nearly all patients with atrial fibrillation (AF) to regulate the ventricular heart rate during AF, reduce or eliminate symptoms, improve hemodynamics, prevent heart failure, and reduce the risk of adverse cardiovascular outcomes [1,2]. Very little robust evidence exists on the type and intensity of rate control management. And while there is increasing awareness that sex is a major determinant in access and response to arrhythmia therapies (Fig. 42.1), studies investigating (non) pharmacological treatments lack adequate representation of the female population [3–5]. Currently, observations are often extended to women in general since predefined sex-specific analyses are frequently missing [4].

Rate versus rhythm control

Randomized controlled trials (Table 42.1)

Two of the largest randomized trials that compared safety and efficacy of rate versus rhythm control approaches were the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study [6,7]. The AFFIRM trial enrolled 4060 patients assigned to either rate or rhythm control. Women accounted for 39% of patients. Amiodarone or sotalol were used in more than two-thirds of patients in the rhythm control group. In the rate control group, β-blocking drugs or digoxin were used in initially nearly half the patients (48.5% and 46.8%, respectively). Primary endpoint was mortality, which did not differ between the groups. Five-year mortality was 23.8% in the rhythm control group and 21.3% in the rate control group (hazard ratio (HR) 1.15; 95% confidence interval (CI) 0.99–1.34, $P = .08$).

The RACE trial enrolled 522 patients randomized to maintenance of sinus rhythm versus rate control. Women accounted for 36% of patients. The primary endpoint (a composite of cardiovascular mortality, heart failure, thromboembolic complications, adverse effects of antiarrhythmic drugs (AADs), and pacemaker implantation) occurred in 17.2% of the rate control group and 22.6% of the rhythm control group (HR 0.73; 95% CI 0.53–1.01, $P = .11$).

The two most recent trials that studied if a rhythm-control strategy with catheter ablation results in an improved outcome compared to conventional drug treatment were the Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) [8] and the Catheter Ablation versus Antiarrhythmic Drug Therapy in Atrial Fibrillation (CABANA) trial [9]. In CASTLE-AF symptomatic patients with paroxysmal or persistent AF and heart failure with a left ventricular ejection fraction of 35% or less were randomized to undergo either catheter ablation (N = 179) or rate- or rhythm control drugs (N = 184). Catheter ablation was associated with a lower rate of the composite endpoint of death from any cause or hospitalization for worsening heart failure than was medical therapy. In CASTLE-AF only 14% were women! This makes extrapolating these data to the female population impossible and should be stressed when implementing these data into clinical practice [8]. CABANA, which randomized symptomatic AF patients to either ablation (N = 1108) or rate or rhythm control drugs (N = 1096) according to contemporary guidelines, failed to show a significant reduction in the primary endpoint of death, disabling stroke, serious bleeding, or cardiac arrest with catheter ablation compared to medical therapy. The secondary endpoint mortality or cardiovascular hospitalization did occur less frequently in the ablation group (51.7% vs. 58.1%; HR 0.83, 95% CI 0.74–0.93). Additionally, patients who received an ablation experienced greater symptom relief and showed more long-term improvement in quality of life compared to patients receiving drugs [10]. 37% of included patients were women. There was no interaction between sex and primary endpoint occurrence or quality of life.

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TABLE 42.1 Randomized controlled trials comparing different rate and rhythm strategies.

Study	Publication year	No. of patients	(%) WWomen versus men	Most important inclusion criteria	Treatment strategy	Primary outcome	Result
AFFIRM [6]	2002	**4060**	**39% W 61% M**	• Age >65 years or risk factors for stroke/death • Likely recurrent AF	Cardioversion and antiarrhythmic drugs versus rate-controlling drugs	Overall mortality	No difference
RACE [7]	2002	**522 63% M**	**37% W**	• Recurrent persistent AF or flutter after previous electrical cardioversion	Cardioversion and antiarrhythmic drugs versus rate-controlling drugs	Composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker, and severe adverse effects of drugs	No difference
RACE II [18]	2010	**614**	**34% W 66% M**	• Permanent AF • ≤ 80 years • Heart rate >80 bpm	Lenient rate control versus strict rate control	Composite of death from cardiovascular causes, hospitalization for heart failure, stroke, systemic embolism, bleeding or life-threatening arrhythmic events	No difference
MANTRA-PAF [12]	2012	**294**	**30% W 70% M**	• Paroxysmal AF • No history of previous antiarrhythmic drug use	Radiofrequency catheter ablation versus class IC or class III antiarrhythmic agents	Cumulative and per-visit burden of atrial fibrillation (i.e., percentage of time in atrial fibrillation on holter monitor recordings)	No difference
RAAFT-2 [13]	2014	**127**	**24% W 76% M**	• Paroxysmal AF • No history of previous antiarrhythmic drug use	Catheter ablation versus antiarrhythmic therapy	Time to first documented atrial tachyarrhythmia of more than 30 s	Ablation compared with antiarrhythmic drugs resulted in a lower rate of recurrent atrial tachyarrhythmias at 2 years (HR 0.56%; 95% ci 0.33 −0.95)
AATAC [11]	2016	**203**	**26% W 74% M**	• Persistent AF • Heart failure NYHA class II or III • LVEF <40% • dual chamber ICD or CRT	Catheter ablation versus amiodarone	Recurrence of AF	Catheter ablation was superior to amiodarone in achieving freedom from AF. Amiodarone therapy failed more often (HR 2.5; 95% CI 1.5−4.3)
CASTLE AF(8)	2019	**363**	**14% W 86% M**	• Symptomatic paroxysmal or persistent AF • Heart failure NYHA class II, III, or IV • LVEF ≤35% • Implanted defibrillator	Catheter ablation versus medical therapy (rate or rhythm control)	Composite of death from any cause or hospitalization for worsening heart failure	Catheter ablation was associated with a lower rate of the composite endpoint (HR 0.62; 95% CI 0.43−0.87)
CABANA [9]	2019	**2204**	**37% W 63% M**	• Symptomatic AF • Age >65 years or ≥1 risk factors for stroke	Catheter ablation versus medical therapy (rate or rhythm control)	Composite of death, disabling stroke, serious bleeding, or cardiac arrest	No difference

AF, atrial fibrillation; *CI*, confidence interval; *CRT*, cardiac resynchronization ratio; *HR*, hazard ratio; *ICD*, internal cardiac defibrillator; *LVEF*, left ventricular ejection fraction; *M*, men; *NYHA*, New York Heart Association; *W*, women.

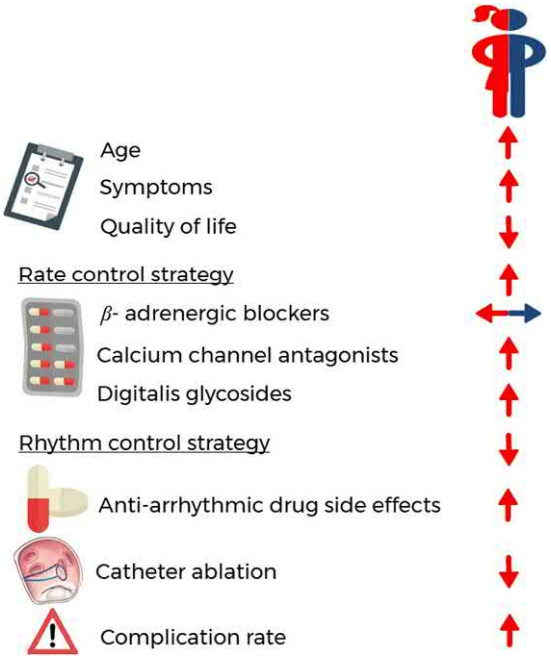

FIGURE 42.1 Sex differences in atrial fibrillation treatment (utilization). Women, who are generally older, tend to have more (atypical) symptoms, a greater symptom burden, and worse quality of life. They are more likely to receive rate control. If pharmacological rhythm control is instituted, they tend to experience more adverse effects. Furthermore, women are less likely to be offered/receive ablation, with possibly more complications if ablation is offered.

Superiority of catheter ablation compared to medical treatment was also studied in the Ablation versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted Device (AATAC) Trial, who showed that ablation of AF (N = 1012) is superior to amiodarone (N = 101) in achieving freedom from AF at long-term follow-up and reducing unplanned hospitalization and mortality in patients with heart failure and persistent AF ($P < .001$). 26% of included patients were women, sex was not univariately associated with AF recurrence [11].

The Medical Antiarrhythmic Treatment of Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) study found no difference in the cumulative burden of AF over 2 years follow-up between radiofrequency ablation (N = 146) compared to AAD therapy (N = 148) as first-line treatment in patients with paroxysmal AF. 30% of included patients were women [12].

The Radiofrequency Ablation versus Antiarrhythmic Drugs as First-line Treatment of Paroxysmal Atrial Fibrillation (RAAFT-2) trial, who randomized treatment-naïve patients with paroxysmal AF to AAD treatment (N = 61) or radiofrequency ablation (N = 66), did find that patients in the radiofrequency ablation group had a lower rate of recurrent atrial tachyarrhythmias at 2 years (HR 0.56; 95% CI 0.35–0.90, $P = .02$). 24% of included patients were women [13].

Sex differences in rate versus rhythm control

There have been limited studies that investigated sex-specific outcomes and complications with rate control and rhythm control strategies. AFFIRM and RACE did investigate differences between men and women (Fig. 42.2).

In the AFFIRM trial, the risk of death did not differ by sex between rate control and rhythm control strategies. Both sexes had a trend toward an increased risk of death in the rhythm control arm versus the rate control group that was not significant [14]. In the RACE study also no major difference in the occurrence of the primary endpoint existed between men (19.1%) and women (21.4%) [15]. However, women in RACE trial receiving a rhythm control strategy experienced a higher incidence of the primary endpoint compared to women receiving a rate control strategy (32.0% vs. 10.5%) (Fig. 42.3).

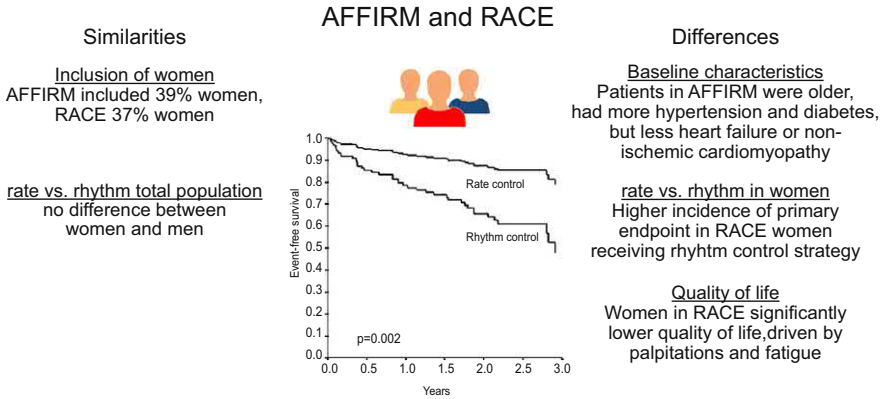

FIGURE 42.2 Similarities and differences between the AFFIRM and RACE trial. Baseline differences existed between the patients included in AFFIRM and RACE. Furthermore, women included in RACE that were randomized to the rhythm control strategy had a worse outcome than women receiving the rate control strategy (Kaplan Meier from Rienstra et al. [15] with permission). This was not observed in the AFFIRM trial. Additionally, women from RACE had a worse quality of life than men, driven mostly by fatigue and palpitations.

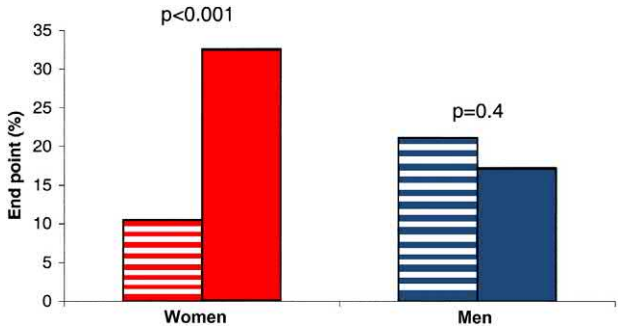

FIGURE 42.3 Sex-differences in primary endpoint occurrence of the RACE trial. Occurrence of the primary endpoint according to sex and randomized strategy (stripped bars = rate control; solid bars = rhythm control). *Adapted with permission from Rienstra M, Van Veldhuisen DJ, Hagens VE, Ranchor AV, Veeger NJ, Crijns HJ, et al. Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the Rate Control versus Electrical Cardioversion (RACE) study. J Am Coll Cardiol October 4, 2005;46(7):1298–1306.*

This was driven mainly by more thromboembolic complications, heart failure, and severe adverse effects of AADs, which consisted mainly of sick sinus syndrome necessitating pacemaker implantation. In men, the incidence of the primary endpoint did not differ between the two treatment groups [15]. Women in the RACE trial had a significantly lower quality of life in both study arms, driven by palpitations and fatigue [15]. Interpretation and clinical translation is limited by different patient selection criteria, the relatively small sample sizes, and a wide range of outcomes without individual event rates. Additionally, the AFFIRM and RACE population differed on some important points. AFFIRM patients were more often aged ≥65 years or older, had more often a history of coronary artery disease (37% vs. 28%), hypertension (70% vs. 43%), or diabetes mellitus (19% vs. 11%), but they were less likely to have heart failure or nonischemic cardiomyopathy (8% vs. 12%). NYHA class II or III also occurred less frequently in AFFIRM patients (8% vs. 52%) [16].

Real-life observational studies, although not explicitly focusing on sex, do confirm that in propensity sex-matched groups the choice of rate or rhythm strategy did not drive clinical outcome differences [17].

Target heart rates

The principal goal of a rate control strategy is to improve symptoms; however, data on the optimal heart rate during AF are limited. Furthermore, rate control measurements during rest alone may not always be sufficient as they do not reflect heart rate changes during daily activities. The AFFIRM investigator used a rate control target of <80 beats per minute at rest. During exercise the target was <110 beats per minute during a 6-minute walk test or a mean heart rate of <100 beats per minute during 24-h Holter monitoring [6]. The RACE investigators used a more lenient approach, targeting a resting rate of less than 100 beats per minute [7].

In a retrospective pooled analysis of both trials, Van Gelder et al. concluded that, despite a lower mean heart rate in AFFIRM (76.1 vs. 83.4 beats per minute), there were no differences between both trials on the primary endpoint of mortality, cardiovascular hospitalization, and myocardial infarction [16]. In total 40% of the combined AFFIRM and RACE cohort were women. Female sex was not associated with composite endpoint occurrence. Patients with mean heart rates during AF within the AFFIRM (≤80) or RACE (<100) criteria had a better outcome than patients with heart rates ≥100 (HR 0.69 and 0.58, respectively, for ≤80 and < 100 compared with ≥100 beats per minute) [16]. From those data, it was concluded that a stringent approach to rate control was not associated with an important difference in clinical events.

This was further investigated in the multicentre, prospective, randomized Lenient versus Strict Rate Control in Patients with Atrial Fibrillation study (RACE II) [18]. 614 patients with permanent AF were randomized to lenient rate control with a resting heart rate target <110 beats per minute or strict rate control with a resting heart rate target <80 beats per minute and a heart rate target <110 beats per minute during moderate exercise performed for a duration corresponding to 25% of the maximal time achieved on bicycle exercise testing. The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. Patients in the lenient group were more likely to receive only β-blocker therapy (43% vs. 22% in the strict rate control group), while patients in the strict rate control group more often received a β-blocker in combination with verapamil/diltiazem or digoxin (38% vs. 20%). Also, the dose of β-blocker was significantly higher in the strict rate control group 169 ± 87 versus 119 ± 81 mg [19].

Lenient rate control was noninferior to strict rate control regarding the development of cardiovascular morbidity and mortality (12.9% vs. 14.9%, $P < .001$ for the prespecified noninferiority margin) [18]. In women and men also no significant difference in primary outcome between lenient and strict rate control was observed, respectively, $P = .31$ and $P = .89$. Furthermore, symptoms, quality of life, and atrial and ventricular remodeling was not significantly different between the lenient or strict rate control group [19,20]. Stringency of rate control did not affect outcome and quality of life. However, symptoms, female sex, age, and severity of underlying disease were associated with a worse quality of life. A lenient rate control, which is easier to achieve and requires less medication, seems to be the most apparent and simple approach in patients with permanent AF.

The women included in RACE II were older and had more accumulation of AF risk factors than men, including more hypertension, heart failure with preserved ejection fraction, poor kidney function, and mitral regurgitation (Fig. 42.4) [21].

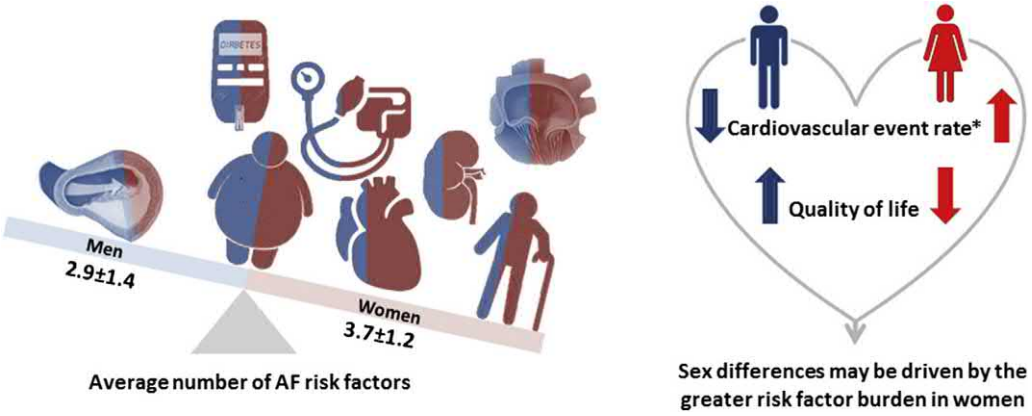

FIGURE 42.4 Sex differences in risk factors in patients from RACE II In the RACE II population, consisting of patients with permanent AF, women had more accumulation of AF risk factors than men. *The observed higher cardiovascular event rate in women was no longer significant after adjusting for the number of risk factors. Further, QoL was negatively influenced by the higher number of risk factors in women. This suggests that sex differences may be driven by the greater risk factor burden in women. Colors in the left panel (red = women; dark blue = men) represent the distribution of risk factors in the RACE II population. *Reproduced with permission from Kloosterman M, Crijns HJGM, Mulder BA, Groenveld HF, Van Veldhuisen DJ, Rienstra M, et al. Sex-related differences in risk factors, outcome, and quality of life in patients with permanent atrial fibrillation: results from the RACE II study. Europace 2019. [Provisionally accepted].*

The observed higher cardiovascular event rate in women was no longer significant after adjusting for the number of risk factors. Additionally, quality of life was lower in women, this remained unchanged during follow-up. Differences in physical functioning and fatigue scales were most pronounced (Fig. 42.5). Quality of life was also more negatively influenced by risk factors in women than in men. Per risk factor baseline SF-36 physical scores decreased by 1.40 in women and by 1.21 in men, $P < .05$.

Notably, women more frequently used β-blocker in combination with digoxin (27% of women and 12% of men), and the prescribed dosages of β-blockade were higher in women receiving lenient rate control than in men (135 ± 84 mg vs. 112 ± 73 mg, $P = .04$) [21]. To what extent treatment disparities reflect actual pathophysiological sex differences remains unknown, but optimal dosing and uptitration in women and men may differ [22].

The question is whether this also holds true in patients with concomitant heart failure with reduced ejection fraction since a lower heart rate is associated with better outcome in patients with *only* heart failure [23,24]. A large individual-patient metaanalysis found that patients with heart failure and AF had no significant reduction in all-cause mortality, cardiovascular hospital admission, or composite clinical outcomes compared with those receiving placebo [25]. This lack of efficacy was noted in all subgroups, including sex and heart rate [25]. It is suggested that patients with heart failure and AF may need higher optimal heart rates at rest and during exercise to maintain a similar cardiac output as patients with heart failure alone, but whether this differs between sexes has not yet been investigated [26]. To conclude, lenient rate control is an acceptable initial approach, regardless of heart failure status, unless symptoms call for stricter rate control [1]. The data available do not suggest that this differs between the sexes.

Sex affecting pharmacotherapy choice

The Euro Heart Survey on Atrial Fibrillation (EHS-AF) analyzed the data of 5333 ambulant or hospitalized AF patients from 182 centers in 35 European Society of Cardiology (ESC) countries. In total, 42% of the included patients were women. The survey showed that women had a greater AF burden and higher heart rate during AF. No difference in prescription rate of β-blockers occurred (49% vs. 41%), but women did receive more digoxin (30% vs. 25%) and less amiodarone (23% vs. 26%). When patients presented with typical AF symptoms, no sex-related difference in the choice of rate or rhythm control was found. However, in the case of atypical symptoms or asymptomatic patients, women were treated more often with rate control (35% vs. 29%) and less frequently received rhythm control compared to men (39% vs. 51%) [27].

The Euro Observation Programme Pilot survey on Atrial Fibrillation (EORP-AF), that included 3119 consecutive in- and outpatients between 2012 and 13 with AF presenting to cardiologists in nine ESC countries, reported the opposite. Women, 40% of the total population, with typical symptoms were more likely to receive rate control than men (33% vs. 26%). However, there was no sex-specific difference in the treatment of asymptomatic patients [28].

The nationwide multicentre Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) enrolled 10.135 patients with incident and prevalent AF at 176 sites in the United States of America. Of the total population, 42% were women. Compared with men, women were more commonly in sinus rhythm at enrollment 37% versus 31%, $P < .001$. Rates of prior treatment with AADs were similar between women and men. No clear mention of sex-specific differences in rate control strategy is mentioned in ORBIT-AF [29].

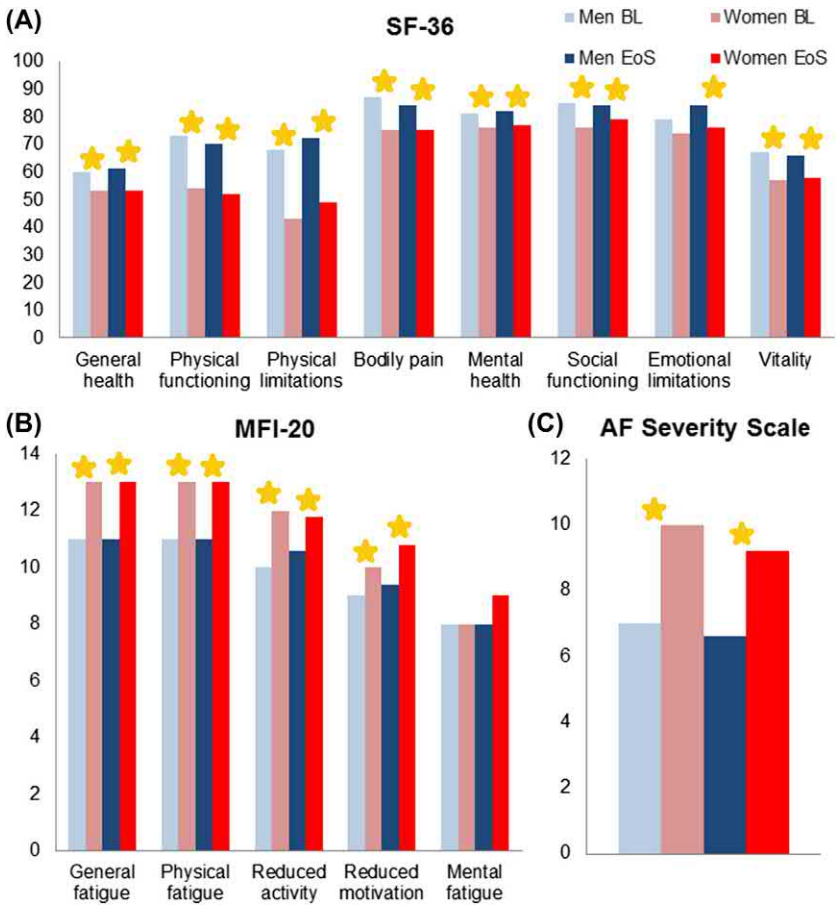

FIGURE 42.5 **Lower quality of life in women included in RACE II** Three quality of life (QoL) scores at baseline (BL) and end of study (EoS) of the RACE II trial: (A) The Medical Outcomes Study Short-Form questionnaire (SF-36), (B) the multidimensional fatigue inventory (MFI-20), and (C) the Toronto AF severity scale (AFSS). SF-36 scores range from 0 to 100, with lower scores representing a lower QoL. MFI-20 scores range from 0 to 35, with higher scores indicating greater AF symptom severity. AFSS score ranges from 4 to 20, with higher scores indicating more fatigue. **P*-values <0.05 between the sexes. Women had a lower quality of life at baseline and end of study, this was most pronounced for physical functioning and fatigue. *Reproduced with permission from Kloosterman M, Crijns HJGM, Mulder BA, Groenveld HF, Van Veldhuisen DJ, Rienstra M, et al. Sex-related differences in risk factors, outcome, and quality of life in patients with permanent atrial fibrillation: results from the RACE II study. Europace 2019. [Provisionally accepted].*

The PREvention oF thromboembolic events—European Registry in Atrial Fibrillation (PREFER in AF) obtained one-year follow up data of 6412 patients with physician-verified AF across seven Western European countries. Of the total population, 40% were women. Adequate heart rate control (defined as 60−100 beats per minute) was comparable in women and men (51.7% and 51.0%, respectively) [30].

The Gulf Survey of Atrial Fibrillation Events (Gulf SAFE) included 2043 patients in six Gulf countries of the Middle East that presented to the emergency room with AF. They report that women, 48% of the total population, were more likely to receive rate control than men (73.8% vs. 63.2%) [31].

Sex differences in prescription of several rate controlling drugs

Rate control, acute or long term, can be achieved by pharmacological slowing of the atrioventricular node conduction using β-adrenergic blocking drugs, nondihydropyridine calcium channel antagonists, digitalis glycosides, or a combination therapy. A number of primary antiarrhythmic drugs, most notably amiodarone and sotalol, have rate-limiting properties, but should only be used in patients needing rhythm control [1]. The specific choice of agent depends on symptoms, clinical circumstances, patient characteristics, and potential side effects. We know there are important differences in the prescription (Table 42.2), adherence, and response of cardiovascular drugs between women and men [32]. However, translation of this information into clinical practice is slow, and evidence-based pharmacodynamic and -kinetic knowledge on sex differences of many cardiovascular drugs and dosages is limited to nonexistent [22].

β-adrenergic blockers

β-blockers are the most commonly used drugs to control ventricular rate during AF. Multiple agents are available,

TABLE 42.2 Sex difference in rate control prescription rates in several large multicentre registry studies.

Study/registry	Country/ world region	Study design	(%) Women versus men	Type of AF (%)			Rate versus rhythm treatment strategy according to symptoms	β-blockers	Calcium channel antagonists	Digitalis glycosides
EHS-AF [27]	European Union	Multicentre, prospective survey	**42% W 58% M**	First detected Paroxysmal (LS) Persistent Permanent	**W** 19 30 21 31	**M** 19 29 24 29	Typical AF symptoms **W = M** Atypical AF symptoms **W ↑** rate control	**W = M**	**W ↑**	**W ↑**
EORP-AF [28]	European Union	Multicentre, prospective survey	**40% W 60% M**	First detected Paroxysmal (LS) Persistent Permanent	**W** 28 29 26 17	**M** 32 25 26 17	Typical AF symptoms **W ↑** rate control Atypical AF symptoms **W = M**	**W = M**	**W = M**	**W ↑**
ORBIT-AF [29]	USA	Multicentre, prospective registry	**42% W 58% M**	First detected Paroxysmal (LS) Persistent Permanent	**W** 5 54 16 25	**M** 5 48 18 29	NA	**W ↓**	**W ↑**	**W ↑**
Gulf SAFE [31]	Middle East	Multicentre, prospective survey	**48% W 52% M**	First detected Paroxysmal (LS) Persistent Permanent Unknown	**W** 30 17 10 40 3	**M** 44 17 9 27 3	**W ↑** rate control	**W ↑**	**W ↑**	**W ↑**
RAMSES [33]	Turkey	Multicentre, prospective survey	**56% W 44% M**	First detected Paroxysmal Persistent/ Permanent	**W** 4 13 83	**M** 6 15 79	NA	**W ↓**	**W ↑**	**W ↑**
Fushimi AF [36]	Japan	Multicentre, prospective registry	**40% W 60% M**	Paroxysmal Persistent Permanent	**W** 51 9 40	**M** 48 9 43	NA	**W = M**	**W ↑**	**W = M**
Swedish study of prescribed drugs [34]	Sweden	Multicentre, primary care registry	**45% W 55% M**	NA			NA	**W = M**	**W = M**	**W ↑**
Scottish Continuous Morbidity Recording Scheme [35]	Scotland	Multicentre, primary care registry	**46% W 54% M**	NA			NA	**W = M**	**W = M**	**W ↑**

AF, atrial fibrillation; *LS*, long standing; *M*, men; *NA*, not available; *USA*, United States of America; *W*, women.

but few studies compare the agents. Metoprolol, propranolol, and esmolol can be administered intravenously in acute situations, but hypotension and bradycardia are important adverse effects. In patients with coronary disease or a myocardial infarction and HFrEF, β-blockers are the preferred agent for rate control [1,2]. In ORBIT-AF, women were less likely to receive β-blocker therapy (62.0% vs. 65.5%, $P < .001$) [29]. This was also observed in the ReAl-life Multicenter Survey Evaluating Stroke prevention strategies in Turkey (RAMSES) study which included 6273 consecutive patients presenting with AF to cardiologists in 57 hospitals in Turkey. They describe that women, 56% of the total population, were less likely to be taking a β-blocker (61.2% vs. 66.2%, $P < .001$) [33].

However, in EHS-AF and EORP-AF no difference in prescription rates of β-blockers was observed between men and women [27,28]. Data from a large primary care registry in Sweden, consisting of individuals aged >45 years and diagnosed with AF in 2002 (1096 women and 1330 men) and 2007 (2234 women and 2748 men), showed no difference in the drug prescription rates of β-blocker agents between women and men in 2002 and 2007 [34]. In the Scottish Continuous Morbidity Recording Scheme which included 3135 patients with AF from 55 primary care practices also no difference in β-blockers use was observed for women (46% of the total population) compared to men (adjusted for practice, age, and deprivation category) [35]. Data from the Fushimi AF Registry, a large community-based prospective survey from Japan that included 3878 AF patients, of whom 40% were women, from hospitals and primary care clinics, reported also no difference in β-blocker use between women and men [36]. The Gulf SAFE study showed different treatment management, with women receiving β-blockers more often than men (37.8% vs. 33.3%, $P < .05$) [31].

Nondihydropyridine calcium channel antagonists

The nondihydropyridine calcium channel blockers verapamil and diltiazem have effects in slowing atrioventricular node conduction and are available in oral and intravenous forms. For acute control of a high ventricular response during AF, intravenous diltiazem and verapamil can be administered with a loading bolus followed by continuous infusion. Calcium antagonists should be avoided in patients with congestive heart failure and left ventricular dysfunction due to their negative inotropic effects [1]. In EHS-AF women received more often diltiazem or verapamil at discharge (10% vs. 8%, $P < .05$) [27]. In the ORBIT-AF registry women also received more often calcium channel blockers (33.0% vs. 28.0%, $P < .001$.%) [29]. This was also observed in the Gulf SAFE registry (16.4% and 10.7% in women and men, respectively, $P < .05$), the RAMSES study (20.0% vs. 26.6%, in women and men, respectively, $P < .001$), and the Fushimi AF registry (12.2% vs. 8.7%, in women and men, respectively, $P < .001$) [31,33,36]. No difference in calcium channel blockers was observed in the EORP-AF registry [28]. In the Swedish and Scottish primary care registries also no sex differences in the drug prescription rates of calcium channel blocking agents was observed [34,35].

Digitalis glycosides

Digoxin acts indirectly on the atrioventricular node by enhancing parasympathetic tone. As such, it may be effective in slowing the ventricular rate during AF in the patient at rest. However, the ability of digoxin to slow the ventricular rate is less during states of exertion when there is vagal withdrawal and enhanced sympathetic tone. Women seem more likely to receive digoxin as a rate control agent. In EHS-AF digoxin/digitoxin was prescribed in 30% of the women at discharge and 25% of men, $P < .01$ [27]. In the EORP-AF registry digoxin was prescribed in 25% of women and 20% of men, $P < .01$ [28]. In ORBIT-AF this was 25% in women versus 23% in men, $P = .02$ [29]. In the Swedish primary care registry women were also more likely to receive digitalis than men 31% versus 20%, $P < .001$ [34]. This was also observed in the primary care registry from Scotland (relative risk (RR) 1.25 for women compared to men; 95% CI 1.07−1.46) [35]. Likewise, in Gulf SAFE and RAMSES women were prescribed digoxin more frequently than men (respectively, 26% vs. 17%, and 22% vs. 19%, both $P < .05$) [31,33]. In the Fushimi AF registry from Japan there was a trend toward women receiving more digitalis but this did not reach statistical significance (13% vs. 11%, $P = .09$) [36].

The higher utilization of digoxin in women may be of concern as is has been associated in some studies, while not in others, with increased mortality in the AF population [37−42]. Recently, a substudy of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial (ARISTOTLE), a randomized double-blind trial that compared apixaban with warfarin in 18.201 patients with AF and at least one additional risk factor for stroke, found that digoxin, especially in serum concentrations >1.2 ng/mL, was independently associated with higher mortality in AF patients, regardless of left ventricular function [43]. This relation between outcome and serum digoxin levels is in line with the original Digitalis Investigation Group (DIG) trial that in a sub-analysis described increased mortality from digoxin levels >1.1 ng/mL [44]. Notably, subanalyses from AFFIRM and RACE II found no significant digoxin−sex interaction on outcome [38,40].

Due to its narrow therapeutic range and toxicity in higher dosages, digoxin should be carefully instituted. Digoxin normally distributes widely to skeletal and cardiac muscle, the kidneys, liver, and intestine. Factors that impact the volume of distribution, including weight (digoxin is hydrophilic and does not significantly distribute into adipose tissue), skeletal muscle mass, renal impairment, and drug−drug interactions, should be taken into account when deciding on the appropriate (loading) dosage for the individual patient [45].

Cardiac glycosides may pose another problem. These medications have long been known to have estrogen-like properties and an increased risk of estrogen-sensitive breast cancer in women receiving cardiac glycosides for AF is described [46,47]. The relationship between baseline AF and development of invasive breast or colorectal cancer was studied in 93.676 postmenopausal women enrolled in the Women's Health Initiative from 1994 to 1998 [46]. After 15 years of follow-up, incidence of invasive breast cancer was 5.7%, and incidence of colorectal cancer was 1.6%. No association between AF prevalence (5.1% in the Women's Health Initiative cohort) and colorectal cancer was found, but an excess risk of invasive breast cancer among those with AF was observed (adjusted* HR 1.19; 95% CI 1.03−1.38, $P = .02$) (* adjusted for age, race, age at menopause, hormone therapy, hysterectomy, and history of cardiovascular disease, among other things). Further adjustment for cardiac glycosides use attenuated that risk (HR 1.01; 95% CI 0.85−1.20). Independent of AF and other confounders, cardiac glycoside use was strongly associated with incident invasive breast cancer (HR 1.68; 95% CI 1.33−2.12) [46]. This association was not observed for other medications including warfarin, antiarrhythmic drugs, aspirin, statins, β-blockers, calcium channel blockers, or angiotensin II receptor blockers.

Another study was a metaanalysis of 14 case−control studies and 15 cohort studies published between 1976 and 2016 [47]. The association between cardiac glycoside use and 13 cancer types was evaluated. The use of cardiac glycosides was associated with a higher risk of breast cancer (RR 1.33; 95% CI 1.25−1.42, $P < .001$). In subgroup analyses an increased risk of estrogen receptor−positive breast cancer but not estrogen receptor−negative breast cancer was found. Glycoside use was associated with increased all-cause mortality (HR 1.35; 95% CI 1.25−1.46, $P < .001$) but not cancer-specific mortality (HR 1.08; 95% CI 0.97−1.19, $P = .18$) [47].

Sex differences in nonpharmacological rate control approaches

Atrioventricular node ablation with pacemaker insertion for rate control can control the ventricular rate when heart failure develops or progresses, patients remain symptomatic, drugs fail, or drug-related adverse effects necessitate drug discontinuation [1,2]. Overall, it should be used as an approach of last resort but it may also be an option early in the management of patients with AF treated with cardiac resynchronization therapy to guarantee sufficient biventricular pacing [48]. ORBIT-AF reports on sex-specific differences regarding atrioventricular node ablation. At baseline women more often had a history of atrioventricular node ablation (2.9% vs. 1.7%, $P < .001$) Furthermore, although overall rates of atrioventricular node ablation during the study were very low, after adjustment female sex was associated with a higher risk for atrioventricular node ablation during the 2.3-year median follow-up (HR 1.97; 95% CI 1.30−2.97, $P = .001$) [29].

In EHS-AF and EORP-AF no difference in pacemaker intervention, performed or planned at registry enrollment, was observed between the sexes [27,28]. Data from the Swedish Pacemaker and Implantable Cardioverter-Defibrillator Registry, which included 700 patients who had undergone atrioventricular node ablation between January 1990 and December 2010, report no sex differences regarding complications, survival, or cause of death. However, regarding system choice, women less often received implantable cardioverter defibrillator devices and/or cardiac resynchronization therapy, despite indications being present [49].

Cardiac function may reduce owing to right ventricular pacing that induces LV dyssynchrony, but results are conflicting and not every person is at risk [50,51]. Progression of the underlying heart disease seems a main factor in the development and deterioration of heart failure, as previous heart failure hospitalization and coronary artery disease, as well as male sex, are described as independent predictors of hospitalization during long-term follow-up [52].

Gaps in evidence and future research and directions

Women are generally underrepresented in (arrhythmia) trials, but data on sex-specific differences in the utilization and outcomes of treatments for AF are accumulating. Based on observations from multiple large registries across the globe (Tables 42.1 and 42.2), we know there are apparent drug treatment differences between women and men with AF (Fig. 42.1).

Women with AF, with an accumulation of risk factors when they age (Fig. 42.6), and a lower quality of life (Fig. 42.4), are more frequently treated with a conservative approach based mainly on rate control [4,5,53−55].

Additionally, women have a tendency to be referred less often than men for management of AF in a specialized outpatient arrhythmia clinic [56]. The observation that

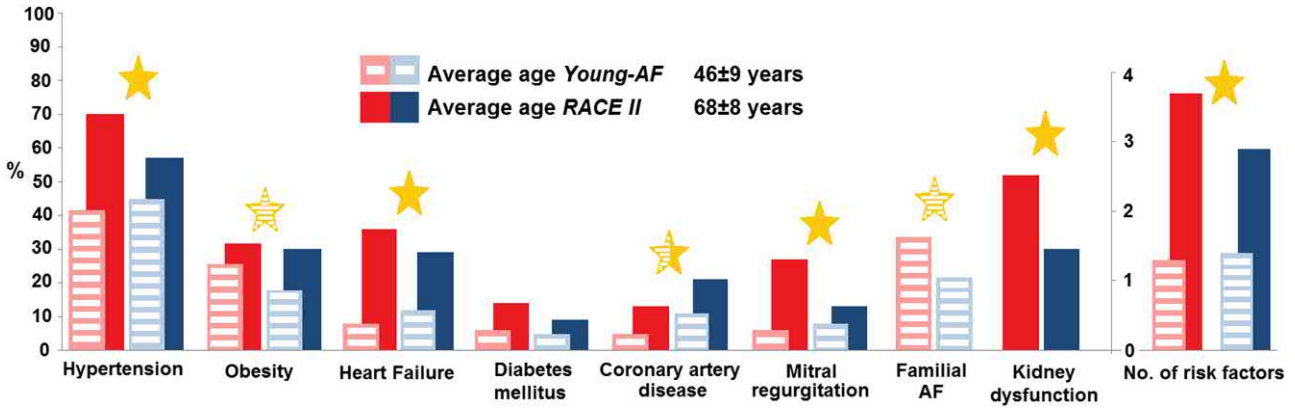

FIGURE 42.6 Accumulation of risk factors in elderly woman—data from YOUNG-AF and RACE II Depicted is the prevalence (%, y-axis) of comorbidities in young patients from the YOUNG-AF cohort [57] (striped pink = women; striped light blue = men) and elderly patients from RACE II(21) (solid red = women; solid dark blue = men). In the younger patients with AF, only familiar AF and obesity occur more frequently in women, while coronary artery disease is more prevalent in men (striped yellow stars). The average number of risk factors does not differ between women and men. In the older RACE II population, women have significantly more risk factors, including hypertension, heart failure, kidney dysfunction, and mitral regurgitation (solid yellow stars). Older men continue to have more coronary artery disease.

rhythm control strategies are pursued less in women than in men, as well as the excess of strokes among women on rhythm control in EHS-AF(27) and the worse outcome of women receiving rhythm control in RACE(15), points toward the need to increase our understanding of these sex-specific differences.

Current knowledge gaps include, among others, (1) the pathophysiological mechanisms that underlie sex-specific differences in outcomes associated with rhythm control strategy, (2) the system-, patient-, and clinician factors that may influence difference in treatment, and the role of stereotypes and unconscious biases, (3) knowledge on sex-specific predictors of outcome including the number of risk factors, and other (bio) markers, and (4) the pharmacokinetic and -dynamic sex differences in the effects of cardiovascular drugs [55].

It seems that a reformation of care and research is warranted to address some of the lacunas in our knowledge. This requires awareness, a revising of research priorities, and adequate patient and doctor education to build a sound evidence base to safely manage women with AF. Systematic reporting of sex-specific results and adequate enrollment of women in future (randomized) AF clinical trials will be important to improve trial generalizability [55]. Additionally, understanding the biological and sociocultural reasons for sex-specific differences will offer opportunities to affect therapy, help reduce the global burden of AF, and may improve prognosis in women [4].

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Chapter 43

Cardioversion

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Atrial fibrillation (AF) is the most common tachyarrhythmia. In the Western world, AF is a major health challenge associated with increased mortality, high morbidity, and growing utilization of health resources [1]. Because of aging of the population, the prevalence of AF is continuously increasing.

The prevalence of AF in the young and middle-aged subjects is lower among women compared to men [2]. However, after menopause, the incidence of AF in women increases. In addition, women typically live longer than men. Thus, in Western countries, in the elderly population, the proportion of females is higher than male. Although the lifetime risk of developing AF is 1.5 to 2 times higher in men, in patients over the age of 75 years, the prevalence of female AF is equal to men if not somewhat higher [2].

The treatment strategy of AF consists of rhythm and rate control. Rhythm control targets to restore and maintain sinus rhythm, whereas rate control aims to control ventricular rate at rest and during exercise and limit the irregularity of heart rhythm despite continuing fibrillation of the atria. Rhythm control is the preferred strategy in patients with severe symptoms, in young patients, in patients with active lifestyle, and in those with reasonable likelihood to maintain sinus rhythm. Rhythm control consists of AF cardioversion (repeated when necessary), antiarrhythmic drug therapy, catheter ablation, surgical ablation, as well as proper anticoagulation.

Women with AF are in general older than men. Compared to men, women have less often coronary artery disease, but they present more frequently other comorbidities such as hypertension, valvular heart disease, diabetes, heart failure with preserved ejection fraction, and are more symptomatic and have lower quality of life [3–6]. In spite of this, women are treated less actively than men. In the ORBIT-AF and PREFER registries, women were less often treated with rhythm control therapy, i.e., less often scheduled for cardioversion and catheter ablation and more frequently undergo ablation of the His node for rate control [6,7]. This reflects also in the AF cardioversion studies in which women are underrepresented. In the large registry studies as well as randomized trials, about two-thirds of patients undergoing cardioversion of AF have been men [6–13] (Fig. 43.1).

Cardioversion is a crucial element of AF rhythm control therapy. However, the topic of cardioversion has been only poorly investigated. Most of the data come from registry studies [6–9,14,15]. Particularly, the effect of sex has been poorly addressed or reported in the existing body of evidence. Thus, there is an unmet need of adequately powered, multicenter, randomized trials evaluating optimal rhythm control and stroke prevention after successful cardioversion to find new methods for AF detection, risk assessment, individualized selection of optimal treatment strategy, as well as pharmacological and nonpharmacological tools for rhythm and rate control and stroke prevention. In addition, the diagnostic tools and therapeutic management should be offered equally to women and men.

Cardioversion of recent-onset AF

Recent-onset AF is defined as paroxysmal AF with duration of <48 h. This refers to the concept that in AF patients the risk of stroke increases with time and patients with AF longer than 48 h are at high risk and should start anticoagulation for at least 3–4 weeks before cardioversion. On the other hand, patients with AF shorter than 48 h bear lower stroke risk and they can be cardioverted with short pre- and periprocedural anticoagulation given during the index admission [16,17]. Recently, the 48-hour safety time window has been disputed [18].

During admission, women with recent-onset AF are more symptomatic and have higher heart rate than men [19,20]. This is likely due to sympathetic predominance of cardiac autonomic regulation among young and premenopausal women and related to sex hormones since there is no significant heart rate difference among girls and boys

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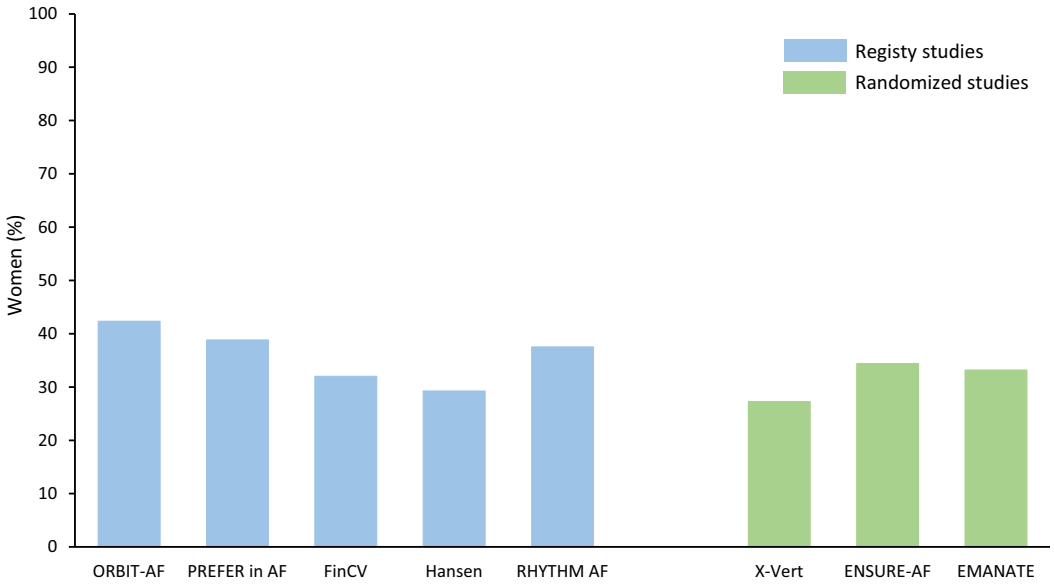

FIGURE 43.1 The proportion of women in registry studies (left bars) and randomized trials (right bars) assessing the risk of stroke associated with cardioversion of atrial fibrillation (AF) [6–9,11–13,15].

before puberty [21] and the heart rate difference diminishes after middle age and menopause [22] and disappears in the elderly [23].

Recent-onset AF can be cardioverted using electrical direct current cardioversion or pharmacological cardioversion. In addition, in about 35%–70% cases of recent-onset AF, conversion to sinus rhythm occurs spontaneously [15,24–26].

Electrical cardioversion is highly effective to restore sinus rhythm in recent-onset AF. The success rate of electrical cardioversion in recent-onset AF is high, 90%–97% [14,15,27]. Most studies in which the efficacy of electrical cardioversion has been evaluated have not addressed the issue of sex and success of AF conversion. In a recent register study in 6.906 electrical cardioversions and 2.868 patients with recent-onset AF, the success rate of cardioversion was 92.9% in women and 94.9% in men [27]. However, after adjustment of confounding factors, the success rate between women and men was not different any more. This is in line with a large international multicenter RHYTHM-AF register in almost 4.000 patients with a recent-onset or persistent AF [15]. It found no difference with respect to the success of electrical cardioversion between the sexes.

Antiarrhythmic drugs, such as intravenous amiodarone, flecainide, ibutilide, propafenone, sotalol, and, most recently, vernakalant, are alternatives to electrical cardioversion of recent-onset AF [14,15,24,28–32]. Cardioversion with oral antiarrhythmic drugs is also possible, but less often used in emergency departments because of slower onset of action. Pill-in-the-pocket at home approach with short acting flecainide is an option in patients with paroxysmal AF after the efficacy and safety have been confirmed in the hospital setting [33].

In the RHTYHM-AF registry, the success of pharmacological cardioversion was 69.1% and female sex was an independent predictor of successful cardioversion to sinus rhythm in patients treated with pharmacological cardioversion [15]. Combining all pharmacological cardioversions, the odds ratio for obtaining sinus rhythm in women was 1.4 compared to men. Using IC class antiarrhythmic drugs, the odds ratio for successful cardioversion was even higher, 2.3. In the studies by Reisinger, pharmacological cardioversion with flecainide, ibutilide, and sotalol also was associated with higher success rate among young women [28,29]. In a recent study, intravenous vernakalant and flecainide were compared [34]. In line with the aforementioned trials, flecainide was more effective to restore sinus rhythm in women compared to men. The success rate with vernakalant also tended (however, nonsignificantly) to be higher among women. The reasons for the higher success rate with pharmacological cardioversion in women have remained elusive. It may be related to differences in cellular electrophysiology between women and men; premenopausal women have higher heart rate, shorter AV nodal refractoriness, longer QT interval, and increased ventricular repolarization heterogeneity [35]. Women also have more pronounced QTc response and higher risk of proarrhythmia with class III antiarrhythmic drugs [36]. Another possible explanation for the higher efficacy of pharmacological cardioversion in women is higher plasma concentration of antiarrhythmic drugs in

women. The dose of drugs used in pharmacological cardioversion is usually weight adjusted. In the case of flecainide and propafenone, the recommended dose is 2 mg/kg with maximum dose of 150 mg. Consequently, a patient weighing 75 kg will be treated with the same dose as a patient weighing 120 kg. Men are heavier than women. Thus, there is a potential risk for underdosing in men.

There seems also to be a difference between the sexes with respect to AF recurrence after successful cardioversion of recent-onset AF. In the study by Grönberg et al., the incidence of early (<30 days) clinical recurrence was 17.3% with the median time to recurrence of AF of 11 days [27]. AF recurrence was significantly higher in women (19.5%) than in men (16.1%), with odds ratio of 1.23. Similar results were reported by Suttorp et al. and Gurevitz et al. [37,38]. In both studies, the recurrence of AF within 12 months after cardioversion occurred in 50% of patients and female sex was associated with increased risk with relative risk of 3.4 and 1.3, respectively.

Arrhythmias, most often bradycardia and sinus arrest, are known complications after AF cardioversion. Bradyarrhythmia (asystole >5 s or sinus bradycardia <40 min) occurred in 0.9% of patients immediately after the electrical cardioversion of recent-onset AF [39], and permanent cardiac pacemaker was implanted in 24 (38%) of them. Female sex increased the risk of bradycardic complications 2.5-fold compared to men in all age groups (Fig. 43.2). Other independent risk factors were old age and unsuccessful cardioversion. Bradycardia can result from drugs used to decrease ventricular rate before cardioversion (beta blockers and calcium channel blockers) or from anesthesia agents. However, in many cases, the bradycardia associated with cardioversion reveals subtle sinus node dysfunction. Abrupt termination of AF with cardioversion and the resulting asystole is a surrogate for sinus node recovery time testing during electrophysiological study. In addition, sinus node dysfunction is known to be associated with increased risk of AF [40].

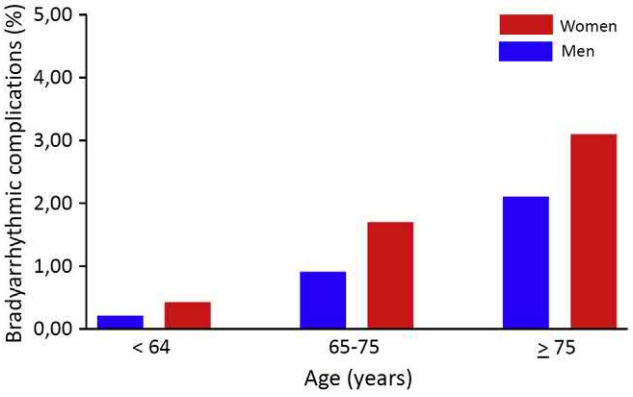

FIGURE 43.2 The incidence of bradyarrhythmic complications according to sex and age. *Modified from Grönberg T, Nuotio I, Nikkinen M, Ylitalo A, Vasankari T, Hartikainen J, et al. Arrhythmic complications after cardioversion of acute atrial fibrillation. Europace 2013;15:1432–5.*

Female sex is included in the CHA_2DS_2-VASc score used in the risk assessment of stroke of patients with permanent AF and no anticoagulation [41]. However, women with AF also present with other CHA_2DS_2-VASc score risk factors for stroke; compared to men, they are older and have more comorbidities. When the confounding factors for stoke were taken into consideration, the risk of stroke in women was not increased compared to men [42,43]. Thus, female sex is not considered to increase the stroke risk in the absence of other stroke risk factors. It is considered as a modifier rather than an independent risk factor for stroke [16].

However, risk stratification of stroke used in permanent AF cannot be applied as such to risk stratification in patients undergoing cardioversion of AF. Namely cardioversion per se increases the risk of stroke. The risk after cardioversion is approximately twofold compared to the background risk of permanent AF in patients on OAC and fourfold in those who are OAC naïve [9,18]. One explanation for the higher risk is atrial stunning. Cardioversion resumes sinus rhythm immediately. However, the contractile function of atria does not recover immediately, but with delay [44]. Depending on the duration of AF, the recovery of atrial contractile function, particularly, in the atrial appendages, can take several days, even weeks [44,45]. As a consequence, a thrombus not present at the time of cardioversion can develop after the cardioversion and embolize after recovery of atrial contractile function, typically 2–3 days after the cardioversion [8]. Another possible explanation for the increased risk after AF cardioversion in anticoagulation naïve patients is that warfarin initiation is associated with a hypercoagulable state and potential clot formation because of significant reductions in protein C and protein S levels. As a result, warfarin initiation increases the risk of stroke during the first days of treatment until the therapeutic INR target has been reached [46].

FinCV study evaluated the risk of thromboembolic complications after 7.660 cardioversion in 3.143 patients with of recent-onset AF [8]. The risk of thromboembolism during the 30 days following the cardioversion was 0.7% in the whole study population but reached 10% in certain patients. Practically same results were reported by a large Danish study with >16.000 patients undergoing cardioversion of recent-onset A [9]. FinCV study also addressed the ability of the CHA_2DS_2-VASc score to predict risk of stroke in patients with and without oral anticoagulation undergoing cardioversion of recent-onset AF [47]. CHA_2DS_2-VASc score was a strong predictor of thromboembolic complications in patients without preprocedural anticoagulation. The risk of stroke during 30-day follow-up after cardioversion in patients with CHA_2DS_2-VASc

score 0−2 was low, less than 0.5%, which corresponds to stroke risk after elective cardioversion in patients on proper oral anticoagulation [11−13,48,49]. On the other hand, the stroke risk was higher and exceeded 1.5% in those with CHA_2DS_2-VASc score >3. Using the same FinCV data, Nuotio et al. studied the impact of time from AF onset to recovery of sinus rhythm and stroke risk [18]. Earlier, it has been considered that the stroke risk increases after 48 h. However, Nuotio found that even within the first 48 h, time was an independent predictor of stroke. AF duration >12 h increased the risk of stroke three- to fourfold compared to cardioversion performed within 12 h from AF onset. Combining the impact of sex, age, and duration of AF, Bah et al. observed that female sex was an independent predictor of thromboembolic complications, with twofold risk compared to men [50] (Fig. 43.3). In patients cardioverted within 12 h, the incidence of thromboembolic complications in women and <75 years was low and did not differ between the sexes. However, in the age group >75 years, the risk of thromboembolic complications increased in both sexes and was significantly higher in women (1.4% vs. 0.9%, respectively). Most strikingly, when cardioversion was performed after 12 h, the risk of thromboembolic complications in women was even higher, two- to fourfold compared to men in all age groups. More recently, Hansen reported that the risk of thromboembolic complications was not different between women and men during 30-day follow-up, whereas the risk was significantly higher among women during 1-year follow-up [9].

Cardioversion of late-onset paroxysmal and persistent AF

Late-onset paroxysmal, in this review, is defined as paroxysmal AF with duration of >48 h but less than 7 days. Persistent AF refers to AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either by electrical cardioversion or with antiarrhythmic drugs [16].

There is solid evidence that women with persistent AF (as well as paroxysmal AF) less often undergo cardioversion than men [5,14,15,51−54].

The success rate of electrical cardioversion to restore sinus rhythm in persistent AF is high, using bipolar chock 92%−95%, with no difference between the sexes [15,38,55]. The success rate of cardioversion using oral antiarrhythmic drugs is significantly lower than with electrical cardioversion, 21%−67%, with amiodarone, dofetilide, flecainide, and propafenone [14,56−59]. Intravenous vernakalant is the most recent antiarrhythmic drug designed for cardioversion of AF. Vernakalant restored sinus rhythm in only 8%−10% of patients with AF duration 8−45 days [31,32]. All these studies were small (8−115 patients) and none of them addressed the efficacy of cardioversion between women and men. Due to lower efficacy, pharmacological method alone is only rarely used for cardioversion of persistent AF. They are used as pretreatment strategy to improve the efficacy of electrical cardioversion and to maintain sinus rhythm after cardioversion [10].

The recurrence of AF after successful electrical cardioversion remains high. In patients undergoing successful cardioversion of persistent AF, the AF recurrence rate has been reported to be 25%−48% within the first month after

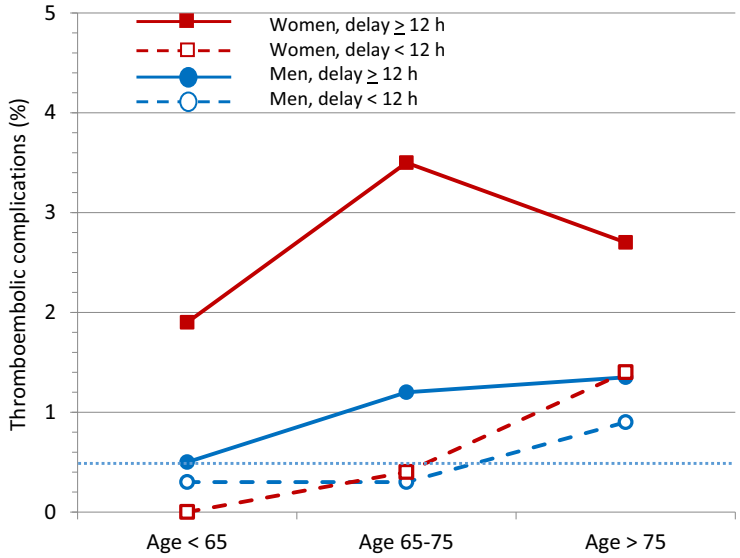

FIGURE 43.3 Thromboembolic complications after cardioversion of recent-onset AF according to sex, age, and time to cardioversion [50].

cardioversion [10,60]. Sex difference in AF recurrence after cardioversion of persistent AF is still somewhat controversial. Gurevitz reported that female sex was an independent predictor of AF recurrence with hazard ratio of 1.3 (Fig. 43.4) [38], whereas this has not been confirmed by others [3,51,54].

Cardioversion of late paroxysmal AF as well as persistent AF must be performed under adequate preprocedural anticoagulation. Thanks to this, the stroke risk is low, less than 0.8% [11−13, 48,49]. All these studies were underpowered to address the impact of sex on stroke risk.

Cardioversion of postoperative AF after cardiac surgery

AF is the most common complication following cardiac surgery. The incidence of new-onset postoperative AF has been reported to range between 20% and 45% after coronary artery bypass graft surgery and is even higher after valve and combined valve and bypass surgery [61]. The peak incidence is between days 2−3 after the surgery [61−63]. The pathophysiology of postoperative AF is not fully understood. Cardiac surgery results in surgical trauma and is often followed by electrolyte disturbances, fluid retention, and sympathetic stimulation. In addition, extracorporeal circulation is associated with systemic inflammatory response, which most likely also plays a role in the development of postoperative AF [64]. The risk of postoperative AF has been reported to be lower among women compared to men [65,66].

Postoperative AF can be cardioverted with electrical cardioversion as well as using antiarrhythmic drugs. In addition, spontaneous conversion of AF to sinus rhythm is common. Up to 80% of patients convert to sinus rhythm within 24 h [67].

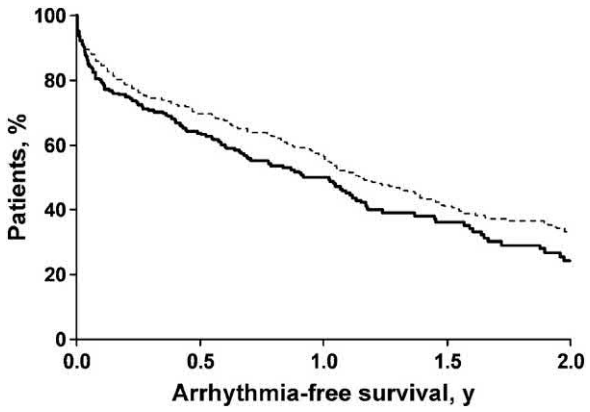

FIGURE 43.4 Arrhythmia-free survival after cardioversion of paroxysmal and persistent atrial fibrillation. The solid line indicates women, and the dashed line indicates men [38].

Electrical cardioversion is effective to restore sinus rhythm is postoperative AF, but the recurrence rate of AF remains high, particularly if cardioversion is performed during the early phase of recovery [68]. Difference in the conversion rate of electrical cardioversion between women and men has been not addressed.

Intravenous amiodarone therapy converts AF within 12−24 h in 40%−90% patients. It is effective in rhythm control after recovery of sinus rhythm and in rate control before the cardioversion [69]. Sex difference in cardioversion success has not been reported (addressed) with amiodarone. Vernakalant is an option for cardioversion of postoperative AF. In a randomized, placebo-controlled study, using intravenous vernakalant the cardioversion rate was 47% with vernakalant and 14% with placebo [70]. In a recent registry study, the success rate with vernakalant was even higher, 76% [71]. Both studies addressed also the impact of sex in the success of cardioversion, but found no difference between women and men. Class Ic antiarrhythmic drugs should be avoided in patients with structural or coronary artery disease because of the risk of proarrhythmia [72].

There is a lack of consensus with respect the optimal practice for the management of AF after cardiac surgery. Recently, Gillinov published a randomized study in which patients with postoperative AF after cardiac surgery were randomized to rhythm control and rate control strategy [61]. After 60 days, the two groups did not differ with respect to the presence of sinus rhythm, thromboembolic complications, or mortality. However, this study did not address the issue of sex and treatment strategy.

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Chapter 44

Catheter ablation of atrial fibrillation

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Introduction

Atrial fibrillation (AF) is the most prevalent cardiac rhythm disorder. The lifetime risk to develop AF according to the ARIC (Atherosclerosis Risk in Communities) cohort is 36% in white men in comparison to 30% in white woman. Lower risk was found for both African American men and women (21% and 22%), respectively [1]. The age-adjusted prevalence of AF is higher in men compared to women; overall prevalence is similar due to higher prevalence in women over 75 years of age [2]. It is estimated that more than 33 million individuals worldwide suffer from AF [3]. AF is significantly related with the risk of stroke [4], heart failure [5], and development of dementia [6]. Moreover, AF increases mortality and risk of sudden cardiac death [7,8]. This arrhythmia is highly symptomatic, causing palpitations, dyspnea, chest pain, fatigue, dizziness, and reduces exercise capacity. It significantly decreases the quality of life [9].

Catheter ablation (CA) of AF has become a part of standard treatment of AF [10,11]. It has been shown in many clinical trials that this procedure is more effective than the antiarrhythmic drugs concerning the rhythm control and maintaining sinus rhythm [12]. In symptomatic patients, the quality of life is improved after CA, which has been demonstrated in multiple studies [13]. In other type of studies, dementia was reduced in patients after CA of AF [14].

Randomized clinical trails comparing major clinical outcomes after ablation of AF were generally lacking. Recently, the CASTLE AF study demonstrated a reduction in death or heart failure hospitalizations in the patients who underwent ablation of AF compared to medical therapy [15]. Furthermore, all-cause mortality alone was also significantly reduced. These patients had heart failure with left ventricular ejection fraction (LVEF) $\leq$ 35% at the time of inclusion. In the CA arm treatment group, the median absolute LVEF increase was 8% at the 60-month follow-up visit compared to 0.2 % increase in the medical arm treatment group. 63% of patients after CA were in sinus rhythm at the 60-month follow-up visit compared to 22% of patient in the medical group. This finding suggests that the maintenance of sinus rhythm is even more beneficial and influencing the prognosis of the heart failure patients with AF. There was no significant difference in the primary endpoint of this study between men and women (who represented 15% of the study population).

This randomized study confirmed findings of previous studies that demonstrated effect of ablation on clinical status and further parameters in heart failure patient with AF. Increase of LVEF, decrease of NYHA class, and biomarkers (e.g., BNP or NT-proBNP) have been repetitively shown [16]. Also in the study of our group in sick patients with long-standing persistent AF and heart failure, we proved significant improvement of "hard" parameters, such as increase of oxygen consumption (VO_2 max) measured by bicycle spiroergometry, increase of left atrial appendage outflow velocity, and decrease of NT-proBNP 12 months after ablation of long-standing persistent AF (Fig. 44.1) [17].

There were huge expectations awaiting the results of further prospective randomized study—the CABANA trial. The AF patients were in this study randomized to ablation of AF or to medical management of AF. The results were presented and published recently [18]. The primary composite endpoint (mortality, stroke, bleeding and cardiac arrest) was not significantly different between both groups through a median follow-up of about 4 years: 8% with ablation and 9.2% with medical therapy (HR 0.86; 95% CI 0.65−1.15). There were some significant differences in secondary endpoints—advantage for ablation for a composite of mortality or cardiovascular hospitalization (51.7% vs. 58.1%; HR 0.83; 95% CI 0.74−0.93) and AF recurrence (49.9. % vs. 69.5%; HR 0.52; 95% CI 0.45−0.60). The quality of life was also improved after ablation of AF. The authors say that the results of the primary intention-to-

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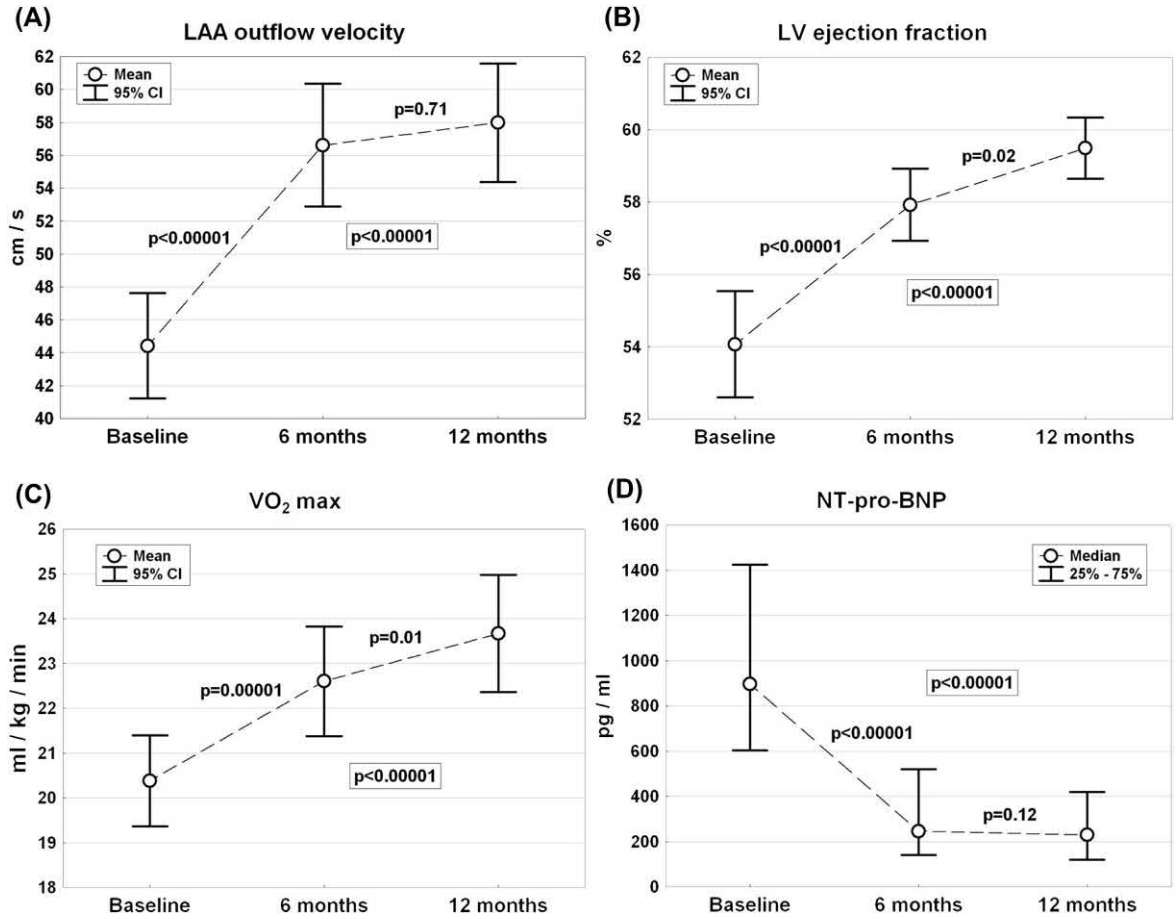

FIGURE 44.1 Results of functional benefits 12 months after catheter ablation in patients with long-standing persistent atrial fibrillation. (A) *LAA*, left atrial appendage outflow velocity; (B) LV left ventricle ejection fraction; (C) VO_2 max, peak exercise oxygen consumption; (D) NT-pro-BNP

treat analysis are inconclusive mainly due to frequent crossovers between the both arms of treatment. They showed low rate of complications of AF ablation.

CA is nowadays well established, effective, and safe treatment of AF, especially in symptomatic patients with paroxysmal forms of AF.

Indications

According to current guidelines and consensus statements, CA is recommended to symptomatic AF patients either as second-line therapy after a trial of at least one or more Class I or III antiarrhythmic drugs or even as first-line therapy in selected patients.

Careful and detailed assessment of individual risks and benefits should always precede indication of this procedure in each individual patient. Both extensive discussion and education of patients and their preferences are very important contributors to the overall success of the procedure. There are some well-known variables that can help with the determination of the anticipated efficacy and probable complications (duration of AF, age, concomitant heart disease, sleep apnea, obesity, size of left atrium).

Generally, the best evidence for indication of AF ablation is in symptomatic patients with paroxysmal AF. There is a Class I recommendation (benefits of CA markedly exceed the risks) for the AF patients as second-line therapy after trial of at least one or more Class I or III antiarrhythmic drugs. It is reasonable to indicate the CA even as first-line therapy (Class IIa recommendation, benefits of CA exceed the risks) in the symptomatic patients with paroxysmal AF.

Recommendations for symptomatic patients with persistent AF (e.g., AF lasting continuously more than 7 days) are not as strong as those for the patients with paroxysmal AF. CA has a Class IIa indication both as the first-line therapy and as the second-line therapy after antiarrhythmic drug failure, it is reasonable to be performed.

Recommendations for symptomatic patients with long-standing persistent AF (e.g., AF lasting continuously more than 12 months) are even weaker. CA may be considered in selected symptomatic patients as Class IIb

TABLE 44.1 Summary of atrial fibrillation (AF) ablation indications.

Clinical type of AF	Therapy	Class of indication	Level of evidence
Paroxysmal	First line	IIa	B-R
	Second line	I	A
Persistent	First line	IIa	C-EO
	Second line	IIa	B-NR
Long-standing persistent	First line	IIb	C-EO
	Second line	IIb	C-LD

Modified from Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace 2018;20(1):e1–e160.

indication (benefits of CA are greater or equal the risks), both as the first-line therapy and as the second-line therapy after antiarrhythmic drug failure.

Indications for several subgroups of patients are the same as described above, including the patients with heart failure, elderly patients, and the patients not well represented in clinical trials (young patients, high-level athletes, patients with hypertrophic or dilated cardiomyopathy, and patients with tachy–brady syndrome).

Recently, several small studies were published describing safety and efficacy of AF ablation in asymptomatic patients [19,20]. There were not any significant differences in the outcome of AF ablations between the groups of symptomatic and asymptomatic patients observed. Thus, AF ablation may be after detailed discussion of the risks and benefits considered even in well-selected asymptomatic patients (Class IIb indication).

Indications for AF ablation are summarized in Table 44.1.

Sex differences in techniques of catheter ablation of atrial fibrillation

There are not any differences in recommendations and indications of CA of AF between men and women.

Techniques

There are two main principles of CA of AF: to eliminate the triggers of AF and to eliminate the substrate of AF. The techniques and strategy used in individual procedure usually combine both of the principles.

Electrical activity in pulmonary veins muscular sleeves has been recognized many years ago as focal trigger for initiation of AF [21]. Therefore, technique of electrical isolation of pulmonary veins was proposed, using either catheter or surgical approach. The initial catheter-based approach targeting focal triggers inside of pulmonary veins moved throughout the years to more and more wider-area circumferential ablation and isolation of pulmonary veins [22]. This approach nowadays dominates, minimizing the risk of pulmonary vein stenosis and targeting even the antral structures outside of pulmonary veins (e.g., ganglionic plexi, nonpulmonary foci)— Fig. 44.2.

Pulmonary vein isolation (PVI) should be a cornerstone and a part of each AF ablation procedure. Unfortunately, achieving permanent PVI is challenging, worsening the outcome of AF ablation procedures and often leading to multiple procedures. PV reconduction is found in repeat ablation procedure in patients with clinical recurrence of AF more often (in more than 80% of patients) [23]. Nevertheless, even in the studies in clinically AF-free patients after initial ablation procedure was reconduction of at least one pulmonary vein found in up to 90% of patients [24].

PVI is mostly being performed by radiofrequency energy catheters using point-by-point circumferential lesion creation, although many single shot devices have been

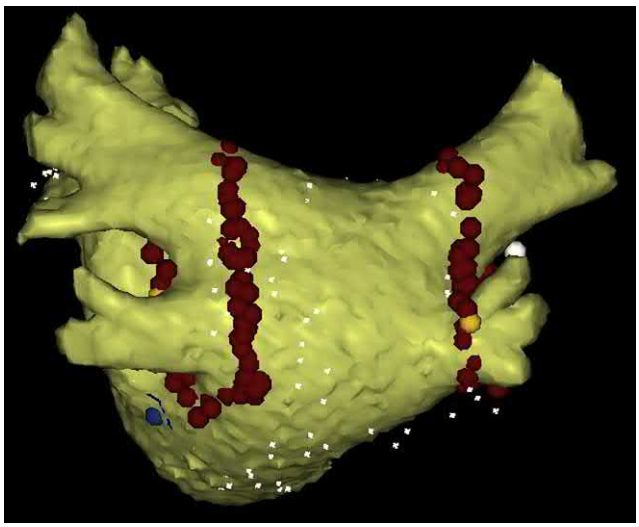

FIGURE 44.2 Circumferential pulmonary vein isolation in patient with paroxysmal atrial fibrillation.

developed and some of them at least partially replaced standard radiofrequency catheters in some centers (namely cryoballoon technology). There is marked progress in the development of radiofrequency catheters as well, enabling measuring of contact force of the tip of the catheter, improving stability, quality, and durability of the lesions [25]. There were studies performed demonstrating both better clinical outcome and lower incidence of PV reconnection when contact-force catheters and ablation index was used [26].

Cryoballoon technique is the most effective alternative to radiofrequency CA. The results of recently published randomized clinical trial FIRE AND ICE showed similar efficacy and safety profile of ablations in paroxysmal AF patients performed either with cryoballoon or radiofrequency catheter [27]. There have been further single shot ablation tools developed (laser balloons, ultrasound systems, multielectrode circumferential ablation catheters), none of them has been widely clinically used yet.

As described above, PVI is a standard part and well-defined endpoint of AF ablation. Elimination and ablation of extrapulmonal vein substrate is much more challenging and various strategies and techniques have been developed and performed to improve the outcome of AF ablations mostly in the persistent or long-standing persistent AF patients.

Additional linear lesions can be created in both left and right atrium, similar to surgical lines used in surgical AF ablations (Cox maze procedures) [28]. The most common lines are the left atrial roof line, mitral isthmus line, and cavotricuspid line. The long-term outcome after using this approach remains controversial, with potential risk of developing macroreentrant tachycardia if the line is incomplete [29]. The current recommendation is not to perform linear lines unless macroreentrant tachycardia is present.

Substrate in diseased fibrotic atria in patients with persistent or long-standing persistent AF is complex, which is represented also by highly fractionated, low-voltage, continuous electrograms (CFAE). Searching for and ablating of CFAE is one of the further strategies, electrogram-guided ablation [30]. Combination of approaches, so-called stepwise approach, has been proposed, endpoint should be termination of AF either to sinus rhythm or to atrial tachycardia by ablation. Although initial outcome was promising, the long-term efficacy after one procedure remains unsatisfactory. Nevertheless, if further ablations are performed, the outcome is improved (62.9% ± 4.5% arrhythmia-free survival at 5 years after mean 2.1 ± 1.0 procedures) [31]. An example of a complex AF ablation of long-standing persistent patient with diseased, low-voltage left atrium is shown in Fig. 44.3.

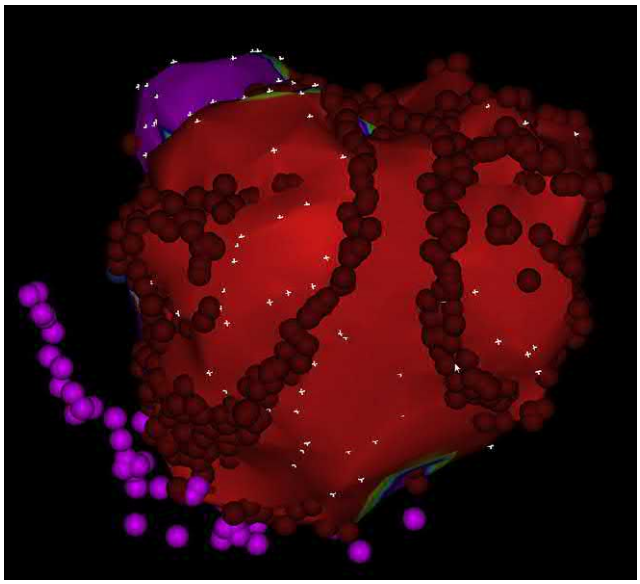

FIGURE 44.3 Complex left atrial ablation in patient with long-standing persistent atrial fibrillation. Red color is representing large low-voltage area.

These findings are concordant with the results and outcome of group of our AF patients. In the analysis of 202 patients with long-standing persistent AF who have undergone AF ablation with stepwise approach, 171 (84%) were in sinus rhythm 12 months after CA (repeated ablation was performed in 30 patients) [32]. The patients in sinus rhythm had significantly better results of their clinical parameters (e.g., peak exercise oxygen consumption, LVEF, NT-proBNP, EQ-5D quality of life measures) in comparison with those patients presented in AF/atrial tachycardia at 12-month follow-up visit (Fig. 44.4).

Atrial fibrosis can be depicted either by sophisticated imaging methods as cardiac magnetic resonance with delayed enhancement or by electroanatomical voltage mapping. There have been ablation strategies presented performing modification and delineation of fibrotic areas, e.g., box isolation.

There are some further ablation strategies applied in persistent AF patients, ablation of ganglionated plexi, ablation areas of rotational activity, some investigators add epicardial ablation. Surgical ablation is very effective method and it is recommended mainly as concomitant procedure in patients with AF indicated for heart surgery.

Sex differences in techniques of catheter ablation of atrial fibrillation

There are not any specific strategies of AF ablation recommended differently to men or women. The same techniques are primarily employed. Nevertheless, there are

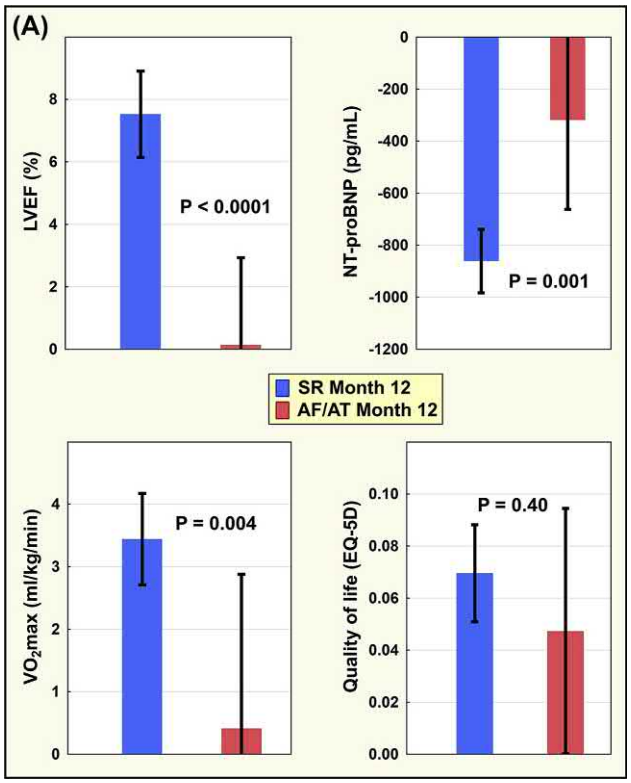

FIGURE 44.4 Results of functional benefits 12 months after catheter ablation in patients with long-standing persistent atrial fibrillation, comparison between patients in sinus rhythm versus patients with atrial fibrillation/atrial tachycardia.

some differences that influence the procedure and the outcome of the procedure.

The left atrial wall in females is generally thinner, achieving of PVI is often faster and requiring less energy. Electrical reconduction between pulmonary veins and left atrium is reported to be lower than in males [33]. Triggers of AF outside of pulmonary veins are more often present in females, causing more frequent recurrences of AF even after successful and durable PVI [34]. The main sources of triggers of extra pulmonary veins are superior vena cava, coronary sinus, and crista terminalis. Repeated ablation targeting even triggers outside pulmonary veins is often indicated; however, very often refused by women due to reluctance to further invasive procedure, satisfactory relief of symptoms, and improvement of the quality of life after first procedure [35]. Atrial fibrosis is more prevalent in women, probably due to older age in the time of ablation [36]. More extensive ablation and substrate modification is often needed. Ablation of atrioventricular node instead of left atrial ablation is more frequently performed in women compared to men [37].

There were 45 women (22.3%) out of 202 long-standing persistent AF patients in the study performed by our group (described above) [32]. In comparison with men, the females were older (63 ± 7 vs. 57 ± 9 years; $P = .0004$), they presented with worse baseline atrial voltage characteristics, lower peak left atrial appendage velocity (38 ± 16 vs. 47 ± 21 cm/s; $P = .2$), lower peak exercise oxygen consumption (15.3 ± 4.1 vs. 21.7 ± 6.0 mL/kg/min; $P < .0001$), and worse quality of life measured by EQ-5D (0.64 ± 0.13 vs. 0.69 ± 0.14; $P = .03$). At 12-month follow-up visit, women presented with lesser improvement of peak exercise oxygen consumption (0.9 ± 3.1 vs. 4.1 ± 4.9 mL/kg/min; $P < .0004$) and LVEF (4.8 ± 8.4 vs. $8.2 \pm 9.2\%$; $P = .046$) in comparison with men, the results of NT-proBNP (-1024 ± 882 vs. -819 ± 787 pg/mL; $P = .182$) lowering and improving of EQ-5D (0.08 ± 0.10 vs. 0.09 ± 0.11; $P = .91$) were comparable. Composite functional SCORE was calculated from relative changes of peak exercise oxygen consumption, LVEF, EQ-5D, and NT-proBNP 12 months after ablation. The SCORE was significantly lower in women compared to men (4.6 ± 2.5 vs. 6.3 ± 2.7; $P = .001$), there was lower proportion of super-responders (SCORE ≥ 8, 15 vs. 36%; $P = .02$) and higher proportion of nonresponders (SCORE ≤ 3, 33 vs. 15%; $P = .02$). The results of SCORE differences between women and men are shown in Fig. 44.5.

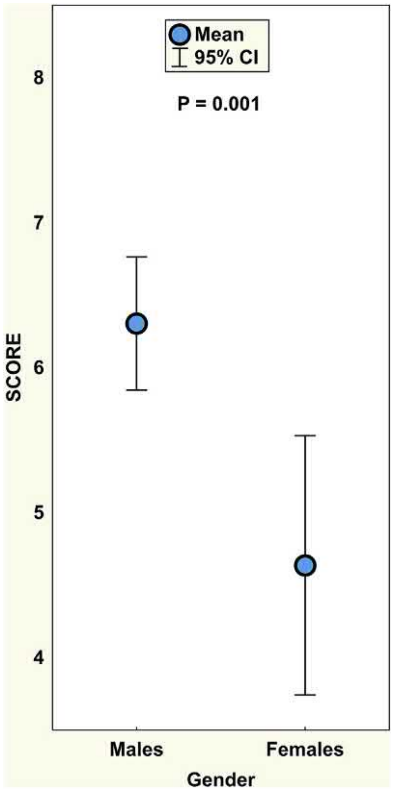

FIGURE 44.5 Composite functional SCORE 12 months after catheter ablation in patients with long-standing persistent atrial fibrillation, comparison between men and women.

General outcomes of AF ablation are discussed in detail in the following chapter of this book.

Complications

CA of AF is a complex electrophysiological procedure. Not surprisingly, it is associated with some risk of complications. The rate of complications decreases over the time, but some of them can be even life-threatening.

It has been repeatedly demonstrated that there are predictors of potential complications both at the patient side (age, comorbidities—heart failure, diabetes mellitus, renal failure, anemia, obesity) and at the operator side (education, low-volume center, training).

According to worldwide surveys, national databases, and registries, the overall incidence of major complications is about 3%−7%. The most frequent are vascular complications (2%−3%), followed by stroke/TIA (about 1%), cardiac tamponade (1%), pulmonary vein stenosis (0.2%), atriooesophageal fistula (0.1%), and permanent phrenic nerve paralysis (0.2%). Periprocedural death was reported in about 0.1%−0.5% of procedures.

Sex differences in complications of catheter ablation of atrial fibrillation

The initial studies and surveys generally reported higher rate of complications of AF ablation in women compared to men. There were 27.821 (32.4%) of women in large database of 85.977 patients in whom the AF ablation was performed between the years 2004−2013. The risk of major complications was about 1.5 higher in comparison with men [38]. Women were more likely to develop vascular complications, tamponade, postprocedural bleeding, acute renal failure, and pneumonia. Higher risk of tamponade was also reported in other multicenter survey, with nearly twofold higher occurrence in women [39]. The risk was lower in high-volume centers.

There are several factors that may explain higher probability of complications of AF ablation in woman. Women are generally older than men at the time of ablation. The left atrial size is smaller, and the left atrial wall is thinner, leading potentially to perforation and cardiac tamponade. The vascular access is more difficult due to higher prevalence of obesity, closer anatomical relationship of femoral artery, and its branches to femoral vein. Female sex is per se risk factor for thromboembolic complications, including cerebrovascular accidents.

Unfortunately, probably at least partially based on above-mentioned facts, there certainly is a referral bias resulting in limited access for AF ablation for women. Women represent only about 20%−30% of AF ablation patients. In contrary, current studies show overall decrease amount of complications, mainly in women. Data from Johns Hopkins group from AF ablations performed between 2001 and 2010 demonstrated higher risk for women, whereas data from AF ablations performed between 2003 and 2015 did not confirm female sex as a predictive factor for complications [40]. The risk of cardiac tamponade is generally lower when using intracardiac echocardiography for the transseptal puncture guidance, both for men and women [41]. Similarly, vascular puncture under ultrasound guidance is safer and associated with lower amount of puncture site vascular complications [42].

Women were thought to be at higher risk of complications of AF ablation compared to men; both the overall risk and the difference can be reduced by modern technology and better experience and knowledge.

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Chapter 45

Demographics and procedural data differences of AF ablation

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Epidemiology

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder, and it is associated with an increased morbidity and mortality [1]. The prevalence of AF increases with age and is higher in men (596 per 100,000) than in women (373 per 100,000) [2]. In particular, in Europe, in subjects older than 55 years, arrhythmia prevalence was 6.0% in male and 5.1% in female [3]. Nevertheless, an American study reported an equal absolute number in the two sexes, due to the longer life expectancy in women [4]. As for Japan population studies, the overall AF prevalence was approximately from half to two-thirds of that in the Western population, with a predominance for male sex [5,6]. Furthermore, it seems that the real epidemiological impact of AF is greater than reported in the prevalence studies, due to underdiagnosis [7].

Clinical presentation and arrhythmia burden

Sex-related differences in clinical presentation, outcome, and management of patients with AF were evidenced in clinical practice [8]. Female patients had higher rate of symptomatic AF, especially palpitations, dizziness, fatigue, and chest pain, thereafter their quality of life (QoL) was significantly lower on the general health, physical role limitations, pain, and vitality than in male patients (see Fig. 45.1). Moreover, women were more likely to have atypical presentation, that might contribute to the worse outcomes seen in female, as they might delay diagnosis and care [9].

Regarding outcomes, studies report a higher AF-related complications rate [stroke and heart failure (HF)] [10] and even a higher mortality in female sex [11]; sex is in itself compared to a true risk factor (see Fig. 45.2). Then, the higher cerebral and systemic thromboembolic risk in women is taken into account in the clinical risk algorithms CHA2DS2−VASc (congestive HF, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65−74 years, sex category) score [12]. Some recent research advise against using sex as a parameter to anticoagulate or not a patient [13,14]: in fact, female sex does not seem to predispose per se to a greater risk of ischemic cardiovascular events, indeed women with a CHA2DS2−VASc score of 1 are usually at a very low risk of stroke [15]. Moreover, it has been recently demonstrated that a greater burden of AF is associated with an increased risk of ischemic stroke: generally women have a lower AF burden [16].

Hormone differences might explain the different AF burden between women and men.

Potential contributions of sex hormones to electrophysiological properties have been explored in some studies. The effects of progesterone were investigated in isolated guinea pig ventricular myocytes [17]. Progesterone seems to modulate delayed rectifier K^+ and L-type Ca^{2+} currents through a nongenomic pathway and it has been associated with shortened action potential and QT interval during the luteal phase of menstrual cycle. On the other side, in rabbit models, estradiol seems to reduce rectifier K^+ currents and increase QT interval [18]. Focusing on human being and on the specific effects of sex hormones in the atria, Rosano et al. [19] conducted a study including menopausal women referred for an electrophysiologic study as a part of a follow-up for radiofrequency catheter ablation. They showed that acute administration of estradiol prolongs right intraatrial and atrioventricular nodal conduction time, as well as right atrial effective refractory period. These observations have been replicated in a female ovariectomy-caused mouse model [20] and confirmed that estradiol has electrophysiologic properties also in vivo and

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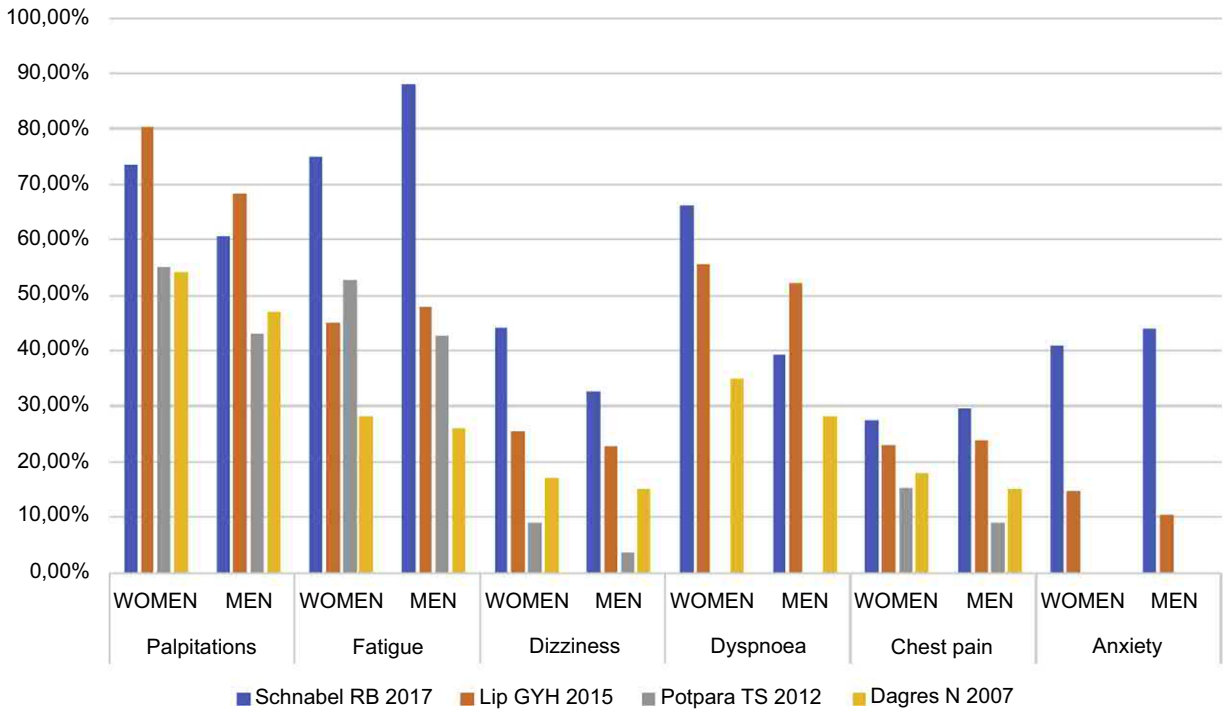

FIGURE 45.1 Symptoms according to the European Heart Rhythm Association classification at baseline by sex. All variables with P value $< .001$. Not significant differences between women and men for fatigue, and dizziness in Dagres study and fatigue, chest pain, dizziness, and dyspnea. *Based on data available on Schnabel RB, Pecen L, Ojeda FM, Lucerna M, Rzayeva N, Blankenberg S, et al. Gender differences in clinical presentation and 1-year outcomes in atrial fibrillation. Heart July 1, 2017 ;103(13):1024–30; Potpara TS, Marinkovic JM, Polovina MM, Stankovic GR, Seferovic PM, Ostojic MC, et al. Gender-related differences in presentation, treatment and long-term outcome in patients with first-diagnosed atrial fibrillation and structurally normal heart: the Belgrade atrial fibrillation study. Int J Cardiol November 1, 2012;161(1):39–44; Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Lévy S, Cobbe S, et al. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. J Am Coll Cardiol February 6, 2007;49(5):572; Lip GYH, Laroche C, Boriani G, Cimaglia P, Dan G-A, Santini M, et al. Sex-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Observational Research Program Pilot survey on Atrial Fibrillation. Europace. January, 2015;17(1):24–31.*

may play a relevant role in facilitating arrhythmias in a variety of conditions. Actually, a single study [21] in a small cohort of women with a history of paroxysmal supraventricular tachycardia reported a significantly higher incidence and longer duration of episodes during the luteal phase of the menstrual cycle (see Fig. 45.3). At the same time, an inverse correlation between serum estrogens' concentration and burden of arrhythmic episodes was observed. Anyhow, whether sex hormones have a direct role in the incidence of AF in women compared with men remains unsure, because most women develop AF at an older age. As for this, hormone replacement therapy in postmenopausal women does not seem to be associated with risk of AF. In the Women's Health Initiative Study [22], after adjusting for incidence of coronary heart disease and HF, no difference was observed in the risk of AF between the group of postmenopausal women randomly assigned to estrogen replacement and the placebo group.

On the other side, in men, lower testosterone levels have been associated with increased risk of AF. In the Framingham Heart Study [23], a significant reduction in testosterone level in men aged $\geq$80 years was associated with a hazard ratio of 3.53 (95% CI 1.69–6.37) in multivariable-adjusted models. An experimental model with gonadectomized male mice confirmed that testosterone deficiency rises atrial arrhythmogenicity, and that its replacement attenuates this effect [24].

As previously mentioned, HF is an important complication in individuals with AF, with discordance in subtypes of HF: men have a higher incidence of HF with reduced ejection fraction, whereas women have a higher risk of HF with preserved ejection fraction [25]. Some studies have established an association between AF and myocardial infarction (MI) [26,27]. Nevertheless, only two studies indicated that the risk of MI was greater in women than in men [26,28].

Atrial fibrillation treatment: focus on catheter ablation

Restoring and maintaining sinus rhythm is an important part of AF management. The clinical benefit of antiarrhythmic pharmacological therapy on stroke and mortality has, however, been questioned: when the rhythm and rate

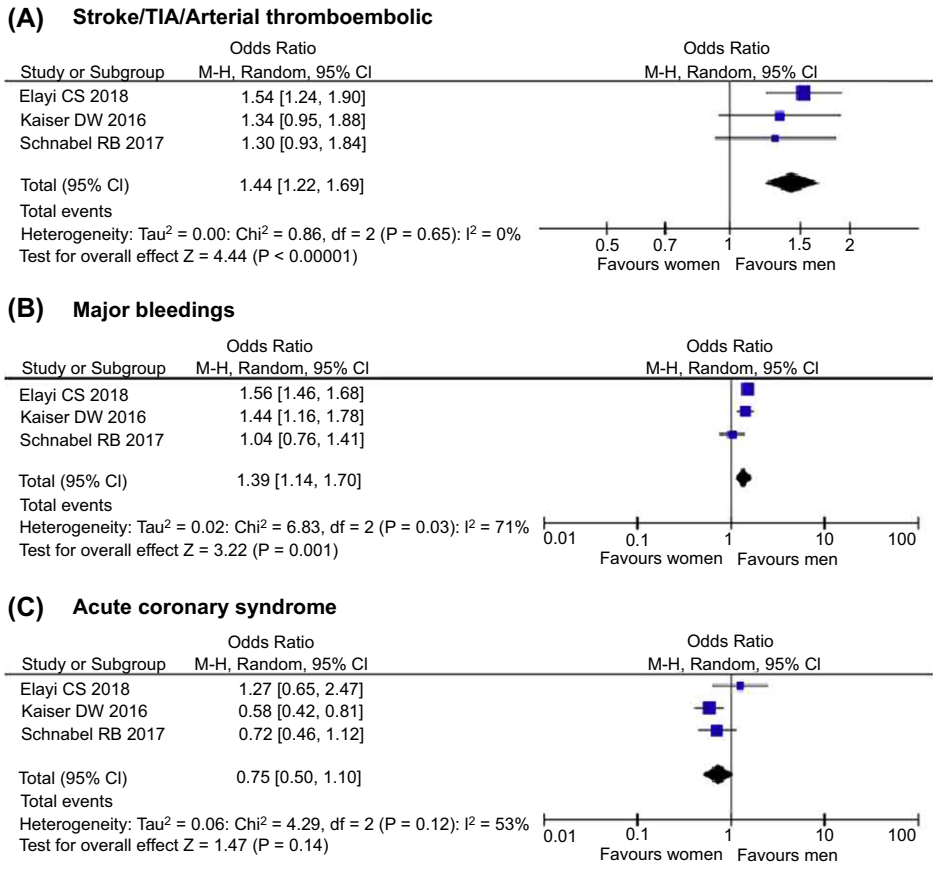

FIGURE 45.2 Age-adjusted women-to-men ORs for 1-year major outcomes. An OR below 1 indicates a lower risk of developing the outcome in women. *TIA*, transient ischemic attack. *Based on data available on Schnabel RB, Pecen L, Ojeda FM, Lucerna M, Rzayeva N, Blankenberg S, et al. Gender differences in clinical presentation and 1-year outcomes in atrial fibrillation. Heart July 1, 2017;103(13):1024–30; Kaiser DW, Fan J, Schmitt S, Than CT, Ullal AJ, Piccini JP, et al. Gender Differences in Clinical Outcomes after Catheter Ablation of Atrial Fibrillation. JACC Clin Electrophysiol 2016;2(6):703–10; Elayi CS, Darrat Y, Suffredini JM, Misumida N, Shah J, Morales G, et al. Sex differences in complications of catheter ablation for atrial fibrillation: results on 85,977 patients. J Interv Card Electrophysiol December, 2018;53(3):333–9.*

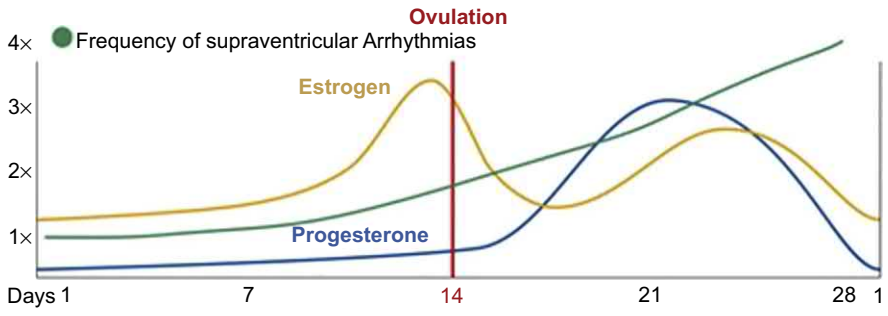

FIGURE 45.3 Incidence of supraventricular arrhythmias during menstrual cycle. *Based on Rosano GM, Kurokawa J, Bai CX, Asada K, Xu J, Oren RV, Zhu ZI, Clancy CE, Isobe M, Furukawa T. Cyclical variation in paroxysmal supraventricular tachycardia in women. Lancet 1996;347:786–8.*

control strategies were compared in the AFFIRM [29] trial, the results seemed to indicate that efforts to restore sinus rhythm do not improve the prognosis. Post hoc analyses showed that patients who stayed in sinus rhythm had more favorable outcome than patients with AF during follow-up [30]. It has been argued that the lack of beneficial effect of pharmacological therapy in the overall study may be due to harmful effects of the antiarrhythmic medication used in the rhythm control arm [31].

Catheter ablation of AF has an important role in the rhythm control strategy and has developed from a specialized, experimental procedure into a common treatment to prevent frequent relapses of the arrhythmia. It is effective in restoring and maintaining sinus rhythm in

patients with symptomatic paroxysmal, persistent, and long-standing persistent AF, in general as second-line treatment after failure of or intolerance to antiarrhythmic drug therapy [32]. However, many studies confirmed ablation as more effective than antiarrhythmic drug therapy (when performed by adequately trained teams in experienced centers), and the complication rate, though not negligible, is similar to the complication rate for antiarrhythmic drugs [33]. The modern technique of AF ablation is based on the milestone observation that paroxysmal AF is often triggered by ectopic atrial activity emerging from the pulmonary veins (PVs) [34] and so can be prevented in a substantial number of patients by electrically isolating the veins. In patients with persistent AF there is evidence of additive benefit in targeting the atrial substrate responsible for AF maintenance in addition to eliminating the PV triggers for AF initiation. On the basis of these data, the electrophysiology community revisited the need for investigating the effect of a more aggressive approach including, in addition to, PV isolation, strategically located linear lesions [35], and the ablation of complex fractionated atrial electrograms [36].

Through the premises and recent guidelines that recommend offering effective diagnostic tools and therapeutic management equally for both women and men [32], a recent review on catheter ablation for AF reported that women referred less often and later than men [37]. As a matter of fact, women with AF are poor represented in all catheter ablation studies. As Table 45.1 shows, they represent less than 25% of patients enrolled in various trials. The causes why women are undertreated remain unclear [38,39], especially considering the worse QoL, the higher AF recurrences after cardioversion—both pharmacological and electrical [40] and the higher risk of side effects due to antiarrhythmic drugs [41].

Differences in procedural aspects

There is no difference in the preablation setting between women and men: management of antiarrhythmic drugs, anticoagulation, and imaging preprocedure (transesophageal echocardiography to exclude thrombus formations, cardiac MRI, or cardiac CT scan for atrial volume estimation and PV visualization) are based on current guidelines [32], hospital protocols, and clinician's preferences. These considerations can be extended to the technical and procedural aspects of ablation of AF: choice of sheaths and catheters, transseptal puncture technique, heparin management, use of fluoroscopy and electroanatomic mapping systems, application of cryo- or radiofrequency-energy, etc.

Focusing on the targets of catheter ablation, several studies demonstrated that PVs are the major site of ectopic beats initiating paroxysmal AF, and isolation of the PVs from the atrial tissue can prevent arrhythmia relapses [34,42]. Non-PV ectopic beats have been proven to start the arrhythmia in some patients, and the presence of non-PV ectopic beats might play a crucial role in the recurrence of AF after PV isolation [43]. A significant difference in the targets between women and men was observed by Patel et al. [44] in a multicenter and retrospective study that enrolled a large cohort of patients ($n = 3265$, 15.8% female). Women had a different distribution of arrhythmogenic triggers, as many of these were not originating from the antral region of PVs and so could be considered more challenging to treat effectively (see Fig. 45.4). As a matter of fact, in this study, women had more failed procedures. Nevertheless, these foci may have affected the outcome not independently but as an aspect of atrial remodeling. Takigawa et al. [45] supported this hypothesis in a recent study that compared the long-term outcome of catheter ablation in patients with paroxysmal AF and different distribution of arrhythmogenic foci: patients with non-PV foci had significantly worse outcomes than other groups. However, in multivariate analysis, the negative impact of these foci appeared to be attenuated, and this factor did not remain as an individual significant predictor.

Differences in outcomes and complications of catheter ablation

There are conflicting data sex-related difference on safety and efficacy of catheter ablation.

Forleo et al. [38] firstly provided a detailed analysis of the sex differences in referral pattern and clinical outcome of ablation in patients with drug-refractory AF. Despite women had a more complex and higher risk clinical profile before catheter ablation (they were generally older and more likely to have hypertension, concomitant structural disease, or a longer history of AF and a larger left atrium), the authors reported similar outcomes in both sexes, with no difference in success, complication, and recurrence rates.

Takigawa et al. [46] reported outcomes of catheter ablation in patients with paroxysmal AF who underwent multiple procedures in a long-term follow-up. Arrhythmia recurrence rate after the first procedure did not significantly differ between men and women but AF recurred more often after the last ablation in women, probably because fewer of them underwent multiple procedures (especially a second one). In fact, women tended to refuse multiple procedures as they were generally more satisfied with the improvement in symptoms after a single procedure, even if AF was not completely eliminated without drugs. Among the patients who did not refuse a second ablation, the efficacy was more than 90% in both sexes.

TABLE 45.1 Baseline characteristics of patients and detailed procedures of analyzed trials.

Trials	No. of patients		Female		LA diameter (mm)		Ablation technique	Drugs	Follow-up (months)
	Ablation	Drug	Ablation	Drug	Ablation	Drug			
Stabile et al. [63]	26	19	12	7	46 ± 5	45.4 ± 5.5	PVI + substrate modification	Class Ic or class III AADs	12
Di Biase et al. [64]	102	101	25	27	47 ± 4.2	48 ± 4.9	PVI + substrate modification	Amiodarone	24
Mont et al. [37]	98	48	22	11	41.3 ± 4.6	42.7 ± 5.1	PVI ± substrate modification	Class Ic or class III AADs	12
Hummel et al. [65]	138	72	23	12	45 ± 5	46 ± 5	PVI ± substrate modification	Class Ic or class III AADs	6
Jones et al. [66]	26	26	5	2	50 ± 6	46 ± 7	PVI ± substrate modification	Beta-blockers and/or digoxin	12
Hunter et al. [67]	26	24	1	1	52 ± 11	50 ± 10	PVI + substrate	Beta-blockers	6
MacDonald et al. [68]	22	19	5	4	–	–	PVI + substrate modification	Beta-blockers and/or digoxin	≥6
Prabhu et al. [69]	33	33	2	4	48 ± 5.5	47 ± 8.2	PVI + substrate modification	Beta-blockers and/or digoxin	6
Shah et al. [70]	627	\	249		\	\	PVI + substrate modification	\	In-hospital
Luik et al. [71]	292	\	116	\	\	\	PVI (RF or CRYO)	\	30
Sindby et al. [72]	21	\	4	\	42.3 ± 3.1	\	PVI + substrate modification (RF or CRYO)	\	12
Yu et al. [73]	113	\	38	\	42.7 ± 5.5	\	PVI ± linear ablation	\	12
Fink et al. [74]	118	\	34	\	47 ± 4.4	\	PVI versus PVI + substrate modification	\	12
Yang et al. [75](2017)	229	\	52	\	49 ± 5.1	\	PVI versus PVI + substrate modification	\	18
Marrouche et al. [76]	179	184	23	29	48	49.5	PVI ± substrate modification	Beta-blockers and/or digoxin and/or class III AADs	60

AAD, antiarrhythmic drugs; *PVI,* pulmonary veins isolation.

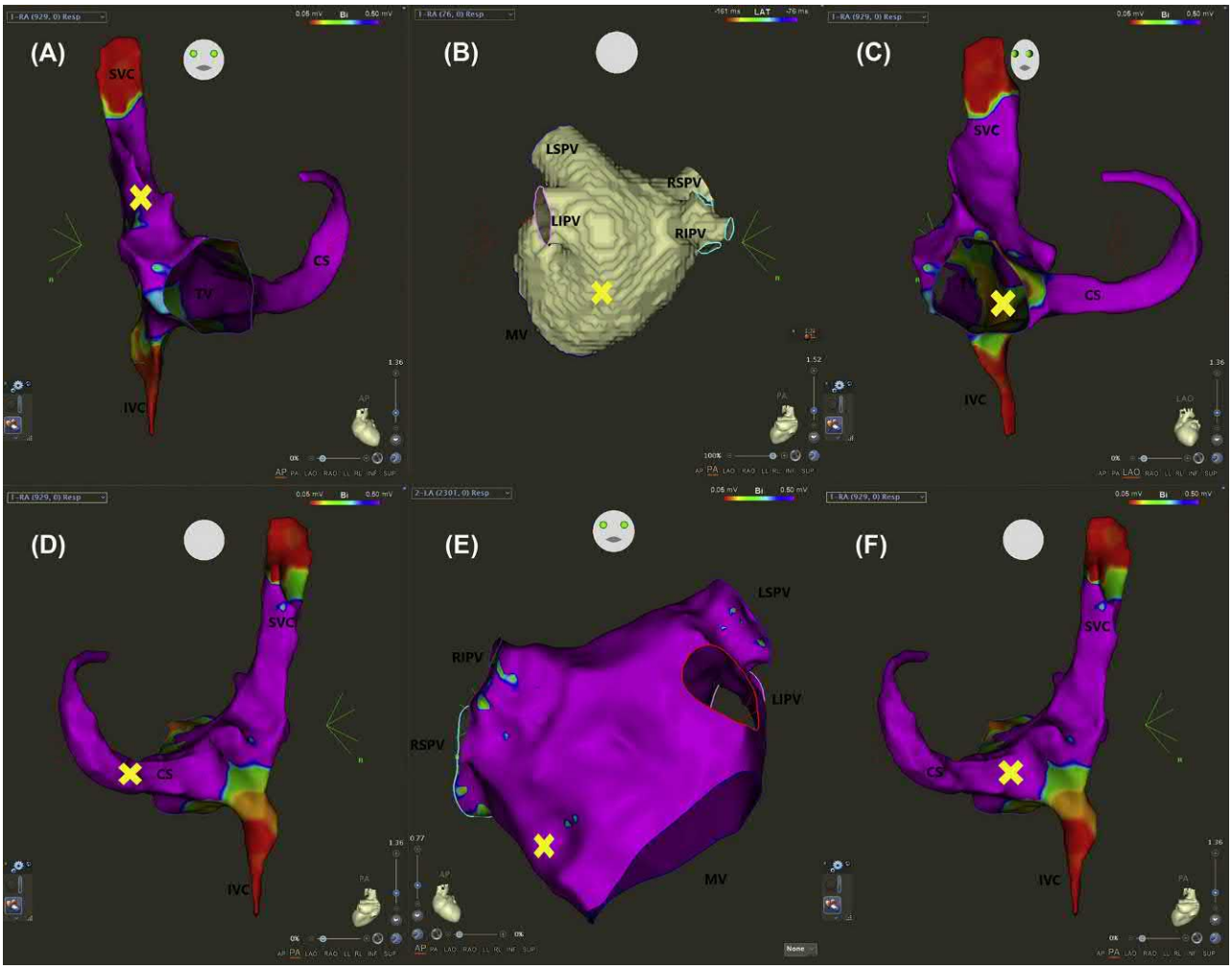

FIGURE 45.4 Nonpulmonary vein ectopic foci initiating paroxysmal atrial fibrillation in female sex. (A) 40% superior vena cava (right atrium in anteroposterior (AP) projection, image obtained by CARTO3 EAM system and right atrium in left anterior oblique (LAO) projection). (B) 34% left atrial posterior free wall (left atrium in posteroanterior (PA) projection, image obtained by CARTO3 EAM system and left atrium in PA projection). (C) 15% crista terminalis (right atrium in LAO projection, image obtained by CARTO3 EAM system and right atrium in LAO projection). (D) 7% ligament of Marshall (right atrium in PA projection, image obtained by CARTO3 EAM system (Biosense Webster, Diamond Bar, CA)). (E) 4% interatrial septum (left atrium in AP projection, image obtained by CARTO3 EAM system and left atrium in PA projection). (F) 1% coronary sinus ostium. (Right atrium in PA projection). *IVC*, inferior vena cava; *LIPV*, left inferior pulmonary vein; *LSPV*, left superior pulmonary vein; *MV*, mitral valve; *RIPV*, right inferior pulmonary vein; *RSPV*, right superior pulmonary vein; *SVC*, superior vena cava; *TV*, tricuspid valve. Of the 94 patients with non-PV ectopic beats, 38 (40%) patients had SVC, 32 (34%) had left atrial posterior free wall, 14 (15%) had crista terminalis, 7 (7%) had ligament of Marshall, 4 (4%) had an interatrial septum, and 1 (1%) had a coronary sinus ostium ectopic beat initiating paroxysmal atrial fibrillation. *(A-F) image obtained by CARTO MERGE, CARTO Segmentation Module and CARTO3 EAM system (Biosense Webster, Diamond Bar, CA); Based on data available on Lee SH, Tai CT, Hsieh MH, Tsao HM, Lin YJ, Chang SL, Huang JL, Lee KT, Chen YJ, Cheng JJ, Chen SA. Predictors of nonpulmonary vein ectopic beats initiating paroxysmal atrial fibrillation: implication for catheter ablation. J Am Coll Cardiol 2005;46:1054–1059.*

As previously reported, Patel et al. [44] showed that women had more non-PV firing sites, failed ablation more often, and had significantly higher bleeding complications (more hematomas and pseudoaneurysms) than men. Outcome results could be attributed to a higher prevalence in female patients of long-standing persistent AF and a longer history of arrhythmia before being considered for the procedure, which may have resulted in increased electrical and structural atrial remodeling. This hypothesis was confirmed by a recent post hoc analysis of the clinical characteristics and outcomes of a group of women undergoing a first persistent AF ablation procedure within MAGIC-AF trial [47]. In this study, women and men had analogous duration of AF from the time of diagnosis and similar left atrial size. Catheter ablation efficacy was similar in the two groups despite the fact that women were older than their male counterparts.

These findings suggest there is no reason to believe that there are differences in outcomes between men and women after catheter ablation of AF when the two populations have

similar comorbidities and are treated at the same stage of disease (Table 45.2). According to this principle, a recent investigation conducted by Walter et al. [48] showed no systematic between-sex differences in human PVs and atrial electrophysiology when stratified by cardiovascular comorbidities known to be associated with atrial remodeling. Clinicians caring for women with AF should be reassured by these data and ensure that women are adequately considered for catheter ablation procedures, especially considering that women with AF have a more impaired QoL and catheter ablation has consistently been proven to be superior to antiarrhythmic drug therapy for maintaining sinus rhythm without the possible toxicity of a long-term pharmacologic therapy [49].

Focusing on the safety of catheter ablation, two recent observational studies [50,51] including a large cohort of patients reported an increased risk of vascular and cardiac complications in women (Table 45.3). They observed not only more hematomas and pseudoaneurysms but also more pericardial effusions and tamponades in women than in their male counterparts. These findings were not previously reported in any of the major AF trials but could be explained with the difference in the intensity of monitoring in a clinical trial setting versus real-life practice.

TABLE 45.2 Clinical data, procedural features, and outcomes (men/women).

Trials		Number of patients	Paroxysmal AF (%)	Persistent AF (%)	Procedure	Repeated procedure (%)	Follow-up (months)	Event-free survival (%)
Forleo et al. [38]	Men	150	61.3	36	PVI + CTI ± LL	14.7	22.5 ± 11.8	82.7
	Women	71	56.3	38		9.9		83.1
Takigawa et al. [46]	Men	864	100	0	PVI + non-PV triggers + CTI ± LL	27.3	39 ± 21.8	81.3
	Women	260	100	0		26.1		76.5
Patel et al. [44]	Men	2747	55	45	PVI + non-PV triggers ± LL ± CFAE	0	24 ± 16	77.5
	Women	518	46	54		0		68.5
Singh et al. [47]	Men	182	0	100	PVI ± CFAE	0	12	58
	Women	53	0	100		0		57

AF, atrial fibrillation; CFAE, complex fractionated atrial electrogram; CTI, cavotricuspid isthmus ablation; LL, linear lesion; PVI, pulmonary veins isolation.

TABLE 45.3 Procedural complications.

Trials		Hematoma (%)	Other vascular complications (%)	Pericardial effusion (%)	Cardiac tamponade (%)	PV stenosis (%)	Stroke/TIA (%)	Death (%)
Forleo et al. [38]	Men	n.s.	n.s.	1.3	1.3	0.7	1.3	n.s.
	Women	n.s.	n.s.	1.4	2.8	1.4	0	n.s.
Takigawa et al. [46]	Men	n.s.	0.1	1.3	n.s.	0.1	0.5	n.s.
	Women	n.s.	0.6	1.8 (includes also cardiac tamponade)	n.s.	0.3	0.3	n.s.
Patel et al. [44]	Men	0.9	0.1	0.29	n.s.	0.4	0.6	n.s.
	Women	2.1	0.6	0.4	n.s.	1.2	0.8	n.s.
Elayi et al. [50]	Men	3.2	0.6	3.5	0.7	n.s.	0.3	0.2
	Women	4.9	1	4.3	1.3	n.s.	0.5	0.3
Kaiser et al. [51]	Men	1.6	2/2.7	n.s.	2.9	n.s.	0.64	0.02
	Women	2.3	2.7	n.s.	3.8	n.s.	0.85	0.07

n.s., not specified.

Although the precise etiology of the higher risk of femoral hematomas or pseudoaneurysms is not clear, it is plausible that three anatomical factors may contribute to these data: (1) the smaller vascular diameter reported in women [52]; (2) anatomic variant more common in women which places the femoral vein underneath the femoral artery and its branches [53]; and (3) a higher proportion of obese among women, a known risk factor for more difficult vascular access [54]. All of them may increase the risk of accidental arterial puncture.

Pericardial effusions and tamponades may occur during transseptal puncture, catheter manipulation, or ablation, with a risk of left atrial perforation being the most common. Tamponade is relatively rare but may be fatal. Surgical backup and acute management skills for treating this complication are crucial in centers performing catheter ablation. Women have a twofold higher risk for developing this complication, but the difference decreases significantly in high volume centers [55]. The risk is higher in women probably because of a smaller left atrial volume and a thinner atrial wall compared to men [56,57]. Women also have a different response to anticoagulant drugs. They show alterations in the pharmacokinetics of heparin which could explain a predisposition to bleeding complications. In particular, women have higher activated clotting times during catheter ablation procedures and so tend to require a lower dose of unfractionated heparin, even after adjusting for weight [58]. Analogous considerations can be made on warfarin response as reported by Humphries et al. in the Canadian Registry of Atrial Fibrillation [9]. Women on warfarin were 3.35 times more likely to experience a major bleeding. INR values at the time of index event were elevated, but the levels were similar in both men and women.

At the same time, women with AF are at a higher overall risk of thromboembolic stroke than men [59]; therefore, it is not surprising to find a trend toward more cerebrovascular symptomatic accidents (TIA/stroke) in women during ablation procedure [59,60]. Meanwhile, no sex-related difference was reported for silent cerebral ischemia lesions detected by magnetic resonance imaging [60]. They seem to be related only to the technologies used (for example, nonirrigated ablation catheters) [61], anticoagulation protocol (including anticoagulation management before procedure, pre-transseptal catheterization intravenous heparin bolus, and ACT over 300 s), long-standing persistent AF, and need for an extensive left atrium ablation [62].

Conclusions

Physicians caring for women with AF should be reassured by these data and ensure that women are adequately considered for catheter ablation procedures, especially considering that women with AF have a more impaired QoL and catheter ablation has consistently been proven to be superior to antiarrhythmic drug therapy for maintaining sinus rhythm without the possible toxicity of a long-term pharmacologic therapy.

AF, atrial fibrillation; *CFAE*, complex fractionated atrial electrogram; *CTI*, cavotricuspid isthmus ablation; *LL*, linear lesion; *PVI*, pulmonary veins isolation.

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Chapter 46

Monitoring and follow-up after atrial fibrillation ablation

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Short-term outcome after catheter ablation of atrial fibrillation

A substantially higher overall rate of periprocedural complications in females compared with males has been consistently reported for various complex invasive cardiovascular procedures, such as pacemaker or cardioverter-defibrillator implantations (8.5% vs. 8.0%), percutaneous coronary interventions (14.8% vs. 9.5%), and catheter ablation (CA) of atrial fibrillation (AF) (8.3%–12.4% vs. 5.6%–9.0%) [1–4].

Several large-scale studies reported sex-based differences in acute and late complications after CA for AF, see Table 46.1 and Fig. 46.1 [3–6]. An analysis of the United States National Inpatient Sample database encompassing 85,977 patients who underwent CA for AF between 2004 and 2013 showed a significantly higher rate of major complications among females compared to males (4.7% vs. 2.7%) [3], owing to a significantly more frequent occurrence of vascular access complications (1.0% vs. 0.6%), cardiac tamponade (1.3% vs. 0.7%), hemodynamically stable pericardial effusion (4.3% vs. 3.5%), cardiogenic shock (0.2% vs. 0.1%), and perioperative hemorrhage (4.9% vs. 3.2%) among female patients [3]. In addition, several serious noncardiovascular intrahospital complications were also more prevalent in females than in males, such as pneumonia (1.4% vs. 0.9%), sepsis (0.4% vs. 0.2%), and acute renal failure requiring dialysis (2.5% vs. 1.5%). Nevertheless, although higher rates of post-CA complications resulted in longer hospital stay in female than in male patients, no difference in short-term death rates was reported [3]. Another large study (the United States Nationwide Readmissions Database analysis of 54,597 patients who underwent CA of AF from 2010 to 2014) reported a 39% relative increase in the risk of any complication and cardiac tamponade, and 49% relative increase in the risk of bleeding or vascular complications in female patients compared to males, even after adjusting for other relevant factors [4].

Cardiac tamponade is the most common fatal complication of AF ablation procedure requiring immediate surgical repair in 15% of the patients and culminating in death in approximately 1% of cases [7–9]. A systematic research that included data voluntarily provided from 19 academic electrophysiology centers on 34,943 CA-AF ablation procedures showed almost twofold higher risk of tamponade in females compared with males (1.24% vs. 0.67%) [6]. Since a reciprocal relationship between operator experience (i.e., center volume) and the risk of cardiac tamponade was also demonstrated, probably females with AF requiring complex CA procedures should be preferentially referred to high-volume centers in order to reduce the risk of serious complications and ensure a more favorable outcome if complications occur [6]. Recent analysis from the German SAFER registry (the Helios atrial fibrillation registry) including 21,141 CA procedures in patients with AF identified several independent risk factors for cardiac tamponade during or immediately after AF ablation procedure and confirmed findings of the previous study [5]. Among other patient-related risk factors (e.g., age, cardiometabolic and/or hepatorenal comorbidities) and procedure-related risk factors (e.g., radiofrequency [RF] ablation technology, low-volume electrophysiology center), female sex was strongly and independently associated with the risk of tamponade (odds ratio, OR 1.63) [5].

The rehospitalizations within the first month after CA of AF are common, and cardiac and noncardiac causes account for 59% and 41% of all the rehospitalizations in this setting, respectively. However, the 30-day all-cause readmission rates were significantly higher among females than males (13.4% vs. 9.4%) [4]. More specifically,

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TABLE 46.1 The studies reporting significant sex-related differences in atrial fibrillation ablation outcomes.

Study	Design	Females versus males					
		Population (n), females versus males	AF type (%)	Clinical differences at CA[a]		Complications (%)[a]	Follow-up	Success rate (%)
Patel [21] (2009)	R., MC.	3265 **(15.8% vs. 84.2%)**[a]	**PAF: 46 versus 55**[a] PeAF: 28 versus 25 **LSPeAF: 27 versus 20**[a]	Age (y) History of AF (y) LAD (mm) AADs failed (n) DM2 (%) HTA (%) CAD (%) Stroke (%)	59 versus 56 6.5 versus 4.8 43 versus 46 4 versus 2 11 versus 15 55.2 versus 40 7 versus 11.3 3.8 versus 1.6	**Any complications: 5 versus 2.4**[a] **Hematomas: 2.1 versus 0.9**[a] **Pseudoaneurysm: 0.6 versus 0.1**[a] Stroke: 0.8 versus 0.6 Pericardial effusion: 0.4 versus 0.29 **PV stenosis: 1.2 versus 0.4**[a]	24 mo	**Index CA: 35.5% versus 68.5%**[a]
Winkle [45] (2011)	R., SC.	843 **(27.9% vs. 72.1%)**[a]	**PAF: 43 versus 28**[a] PeAF: 46 versus 52 **LSPeAF: 11 versus 20**[a]	Age (y) HTA (%) LAD (mm) Dilated CMP (%) Failed ≥1 AAD (%) Pacers/ICDs (%)	66 versus 60 50 versus 40 40.5 versus 44.2 3.4 versus 9.4 79.1 versus 68.4 10.2 versus 5.2	Major complications: 2.6 versus 1.7 Minor complications: 2.0 versus 1.3	2.4 y	Index CA (at 2 y): 48.2% versus 52.6% **Multiple CAs (at 2 y): 67.1 versus 76.3%**[a]
Zhang [37] (2013)	P., SC.	220 **(33.2% vs. 66.8%)**[a]	LSPeAF in all	Lone AF (%) Rheumatic HD (%) AADs failed (n) Amiodarone (%)	27.4 versus 47.6 19.2 versus 1.4 2.8 versus 2.5 26 versus 14.3	**Hematomas: 6.8% versus 0.7%**[a] Pericardial effusion: 1.4 versus 1.4	19 mo	**Index CA: 35.6% versus 57.1%**[a] Redo CA included: 54.8% versus 66.0%
Takigawa [36] (2013)	R., SC.	1124 **(23.1% vs. 76.9%)**[a]	PAF in all	Age (y) BMI (kg/m^2) CAD (%) HCM (%) Mitral stenosis (%) LADI (mm/mm^2) LV EF (%)	63.2 versus 60.0 23.2 versus 23.7 2.7 versus 7.3 6.2 versus 2.7 3.1 versus 0.6 24.4 versus 21.6 68.6 versus 65.6	Any complication: 4.1 versus 3.7 **Vascular injury: 0.3 versus 0.1**[b] Cardiac tamponade: 1.8 versus 1.3 TIA/stroke: 0.3 versus 0.5 Phrenic nerve injury: 0.6 versus 0.4 **PV stenosis/injury: 0.59 versus 0.1**[b]	39 mo	Index CA (at 3 y): 60.8% versus 66.1% **After final CA (at 3 y): 79.2% versus 86.8%**[a]

Kaiser [10] (2016)	R., MC.	20,091 (29% vs. 71%)[a]	Not available	Age (y) CHA_2DS_2-VASc (n) HTA (%) DM (%) Stroke/TIA (%) MI (%) Anemia (%) Amiodarone (%)	62 versus 58 2.9 versus 1.6 66.2 versus 61.8 22.8 versus 20.7 5.7 versus 3.5 4.5 versus 5.6 13.6 versus 8.2 13.9 versus 16.0	**Vascular lesion: 2.7 versus 2.0** **Hematoma/bleeding: 2.3 versus 1.6** Pneumo/haemato-thorax: 0.13 versus 0.14 **Tamponade: 3.8 versus 2.9**	1 y	**Freedom from AF rehospitalizations after index CA: 86.6% versus 89%**[a]
Yu [39] (2018)	R., SC.	1060 (<60 y of age) (21% vs. 79%)[a]	PAF, 71%	Age (y) BMI (kg/m^2) Heart failure (%) HTA (%) DM (%) CHA_2DS_2-VASc (n) LAVI (mL/m^2) LA voltage (mV) HRV (rMMDS)	50.8 versus 49.5 23.8 versus 25.5 12.1 versus 7.2 26.0 versus 36.0 4.9 versus 10.0 1.6 versus 0.8 36.8 versus 33.0 0.99 versus 1.32 28.5 versus 21.4	Major complications: 0.9 versus 2.0 Femoral AV fistula: 0 versus 0.2 TIA/stroke: 0 versus 0.4 Hemato-pericardium: 0.4 versus 1.3	24.5 mo	**Index CA: 61% versus 73%**[a] **Second CA: 50.0% versus 71.8%**[a]
Kuck [38] (2018)	P., MC.	750 (38.7% vs. 61.3%)	PAF in all	Age (y) GFR (ml/min/$1.73m^2$) CAD (%) HTA (%) LAD (mm) Heart failure (%)	64 versus 57 74 versus 82 5 versus 10 62 versus 55[b] 39.9 versus 41.2 34 versus 24	**Any complication: 15.7 versus 9.8**[a] **Groin site complication: 4.8 versus 2.0**[a] Cardiac tamponade: 1.4 versus 0.4 Stroke/TIA: 0.7 versus 0.4	1.5 y	**Female sex was associated with a 37% higher risk of arrhythmia recurrence**
Cheung [4] (2019)	R., MC.	54,597 (37.8% vs. 62.2%)[a]	Not available	Age (y) Heart failure (%) CAD (%) HTA (%) Obesity (%) Stroke (%) Valvular HD (%) Anemia (%)	68 versus 62 19.2 versus 15.7 21.8 versus 29.2 60.4 versus 56.6 16.8 versus 15.2 7.7 versus 5.0 16.6 versus 11.5 8.9 versus 4.0	**Any complication: 8.3 versus 5.6**[a] **Vascular complications: 5.6 versus 3.4**[a] Pneumothorax: 0.26 versus 0.2 **Cardiac perforation: 2.2 versus 1.6**[a] CNS complications: 0.34 versus 0.23	1 mo	30-day all-cause readmissions: 13.4% versus 9.4% **30-day AF/AT readmission rate: 3.9% versus 2.8%**[a]

AAD, antiarrhythmic drug; *AF*, atrial fibrillation; *AT*, atrial tachycardia; *AV*, arterio-venous; *BMI*, body mass index; *CA*, catheter ablation; *CAD*, coronary artery disease; *CMP*, cardiomyopathy; *CNS*, central nervous system; *DM*, diabetes mellitus; *GFR*, glomerular filtration rate; *HCM*, hypertrophic cardiomyopathy; *HD*, heart disease; *HRV*, heart rate variability; *HTA*, hypertension; *ICD*, implantable cardioverter-defibrillator; *LAD*, left atrial diameter; *LADI*, left atrial diameter index; *LAVI*, left atrial volume index; *LSPeAF*, longstanding persistent atrial fibrillation; *LV EF*, left ventricular ejection fraction; *MC*, multicenter; *MI*, myocardial infarction; *P*, prospective; *PAF*, paroxysmal atrial fibrillation; *PeAF*, persistent atrial fibrillation; *PV*, pulmonary vein; *R*, retrospective; *SC*, single -center; *TIA*, transient ischemic attack.

[a]*Statistically significant difference* ($P < .05$).

[b]*Difference tended to be significant.*

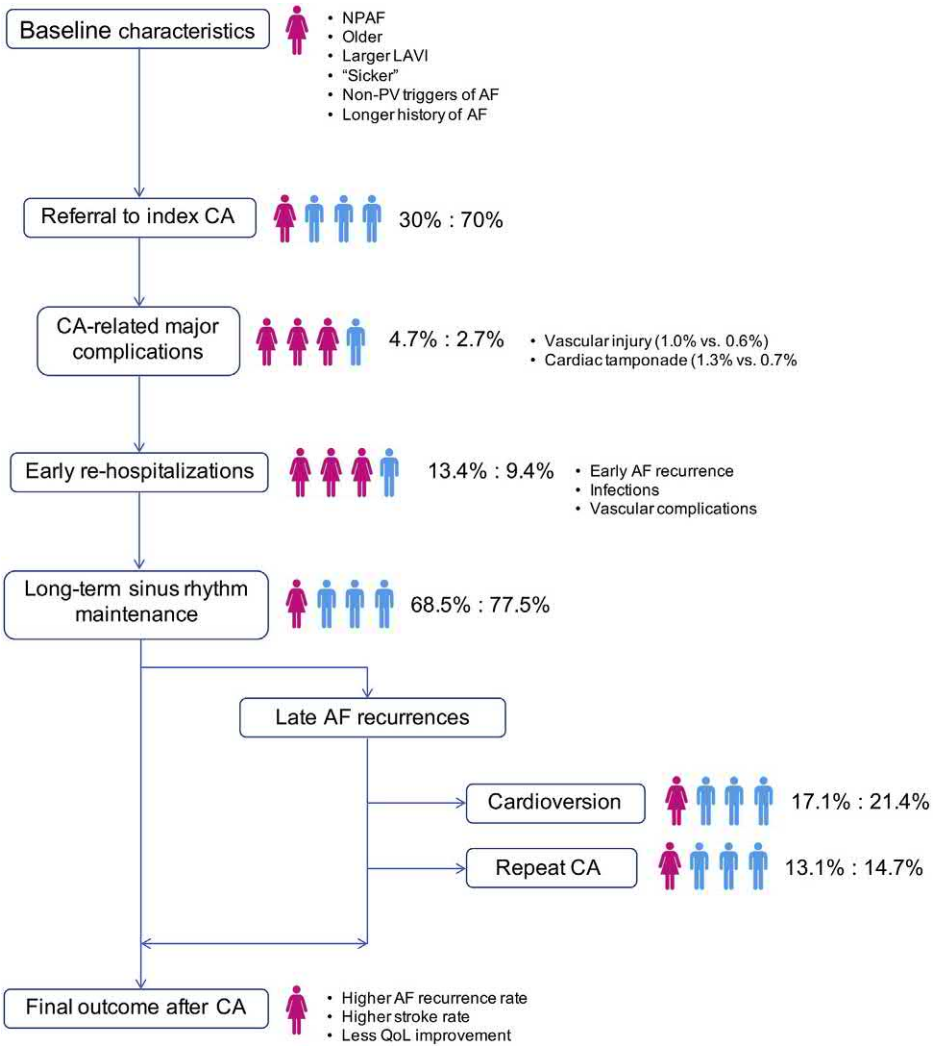

FIGURE 46.1 Sex-related differences in referral and outcome among patients undergoing CA of AF. *AF*, atrial fibrillation; *CA*, catheter ablation; *LAVI*, left atrial volume index; *NPAF*, nonparoxysmal atrial fibrillation; *PV*, pulmonary vein; *QoL*, quality of life.

females had more frequent readmissions for the early recurrence of atrial tachyarrhythmia (OR 1.44), cardiac causes such as congestive heart failure (OR 1.54), and noncardiac causes such as infectious, gastrointestinal, or vascular complications (OR 1.34) [4]. In line with these findings, another large report demonstrated that females (vs. males) had a trend toward increased all-cause 30-day hospitalizations (9.4% vs. 8.6%) and stroke (0.85% vs. 0.64%), as well as significantly increased 30-day rates of vascular complications (2.7% vs. 2.0%), hematomas/bleedings (2.3% vs. 1.6%), and cardiac tamponade (3.8% vs. 2.9%) [10].

Certain important sex-related differences in vascular anatomy may explain the difference in reported complication rates in males and females. Females have significantly shorter femoral artery (37.9 ± 12.7 mm vs. 46 ± 17.2 mm) and a smaller vessel caliber [11], as well as a higher prevalence of obesity (16.8% vs. 15.2%) [4], all of which may increase the risk of vascular access site complications such as inguinal hematoma, femoral arteriovenous fistula, or femoral artery pseudoaneurism [3,4,11,12]. A more common finding of atrial septum aneurism among females (female-to-male ratio of 2:1) [13] may result in more challenging transseptal puncture [14] with increased risk of cardiac or aortic root perforation in females. At CA procedure, females are older and "sicker" than males, with higher prevalence of comorbidities such as hypertension, diabetes, anemia, and renal failure that increase the risk of an invasive cardiac procedure [3]. In addition, females have a higher activated clotting time compared to males, even after administration of lower weight-adjusted dose of unfractionated heparin [15], potentially increasing the risk of major periprocedural bleeding [3–6,9–12]. Smaller absolute dimension of the left atrium (LA), thinner LA

wall, and sex-based biological disparities of tissue response to (RF) ablation [16,17] could be responsible for higher incidence of perforation, tamponade, and pericardial effusions in females during active catheter manipulation as well as during RF delivery for ablation [3–6,9,11,18]. At presentation, females have a more advanced stage of atrial remodeling [19], a higher prevalence of low-voltage areas within the LA [20], and, consequently, they have a nonparoxysmal type of AF [21] more often than males, thus requiring an extensive LA ablation on top of pulmonary vein (PV) isolation, which may further prolong the procedure and anesthesia time and increase the risk complications.

A sex-based subanalysis of AF ablation outcome reported considerable difference among independent predictors of major procedural complications between females and males [3]. While previous history of peripheral vascular disorders and anemia were independently associated with more common occurrence of major complications post-CA in both sexes, chronic renal failure (OR 3.79), history of cerebrovascular accident (OR 1.77), obesity (OR 1.68), and coronary artery disease (OR 1.60) were shown to be independent predictors of major complication specifically in female but not in male patients undergoing CA of AF [3].

Long-term outcome after atrial fibrillation ablation

CA of AF is superior to antiarrhythmic drugs for long-term clinical control of the arrhythmia, particularly in highly symptomatic patients [12,22–24] and in selected patients with heart failure [25]. However, depending on the presence of comorbidities, stage of arrhythmia substrate disease, and duration/intensity of postprocedure rhythm monitoring, the arrhythmia recurrence rate after index ablation is high, varying between 30% and 70% and requiring multiple CA procedures in one out of four to five patients [26,27].

Early recurrences of atrial arrhythmias during the first 3-month blanking period after CA of AF are particularly common, being only transient in a half of patients as a result of ablation-related thermally induced inflammatory injury of atrial tissue, which may spontaneously diminish in the following weeks [27]. Therefore, by consensus, the final rhythm outcome of CA should be assessed only after this early postablation period [12,26].

Almost 70%–90% of the late recurrences of atrial arrhythmias occurring after the blanking period are detected before the end of the first post-CA year, see Fig. 46.2 [28]. However, at each subsequent year of follow-up, a very late atrial arrhythmia recurrence affects 9%–16% of previously arrhythmia-free patients. As the time from CA to the arrhythmia recurrence prolongs, the relative importance of late PV reconnections for AF recurrence seemingly decreases, while the role of progressive atrial remodeling (outside the PVs) become more important [29–31]. The LA enlargement, nonparoxysmal type of AF, early arrhythmia occurrence within the blanking period, presence of structural heart disease and/or cardiometabolic comorbidities, aging, obesity, alcohol consumption, sleep apnea, elevated serum markers of inflammation, and substantial atrial fibrosis are well-recognized risk factors for the arrhythmia recurrence late after CA of AF [27,30–34].

Sex-related differences in rhythm outcome after the index procedure

Postablation follow-up studies reported conflicting results regarding sex-related differences in long-term CA efficacy. While several studies reported higher rates of late arrhythmia recurrence in females compared with males [10,21,35–37], other reports found similar CA efficacy in both sexes [26].

A large multicentre retrospective study of 3265 patients undergoing AF ablation found significantly lower success rate of the procedure among females during the 2-year follow-up (68.5% vs. 77.5%), see Table 46.1 and Fig. 46.1 [21]. The procedure failure in females was independently associated with obesity (body mass index over 30 kg/m^2), nonparoxysmal AF at presentation and non-PV arrhythmia triggers [21]. Several smaller studies confirmed these findings [36,37].

Among patients with paroxysmal AF, female sex (vs. male sex) was recently associated with almost 40% higher risk of primary efficacy failure, defined as the composite of atrial arrhythmia recurrence, prescription of antiarrhythmic drug(s), or repeat CA [38]. These observations were consistent regardless of technology used for PV isolation (i.e., RF point-by-point ablation or cryoballoon single-shot ablation) [38]. Interestingly, the susceptibility of females to recurrence after CA of AF may be significantly mediated by aging [39,40]. In comparison to age-matched male patients, the recurrence rate after AF ablation was higher among females under 55 years of age, but was lower among those older than 75 years than in their male counterparts [40].

There could be a different timeframe of arrhythmia recurrences between the sexes. Whereas several clinical scoring systems (e.g., the ATLAS, CAAP-AF, and PLAAF scores) that were proposed for the AF outcome prediction after CA identified female sex as a risk factor strongly linked with AF recurrence after blanking period [41–43], the MB-LATER score, which was originally

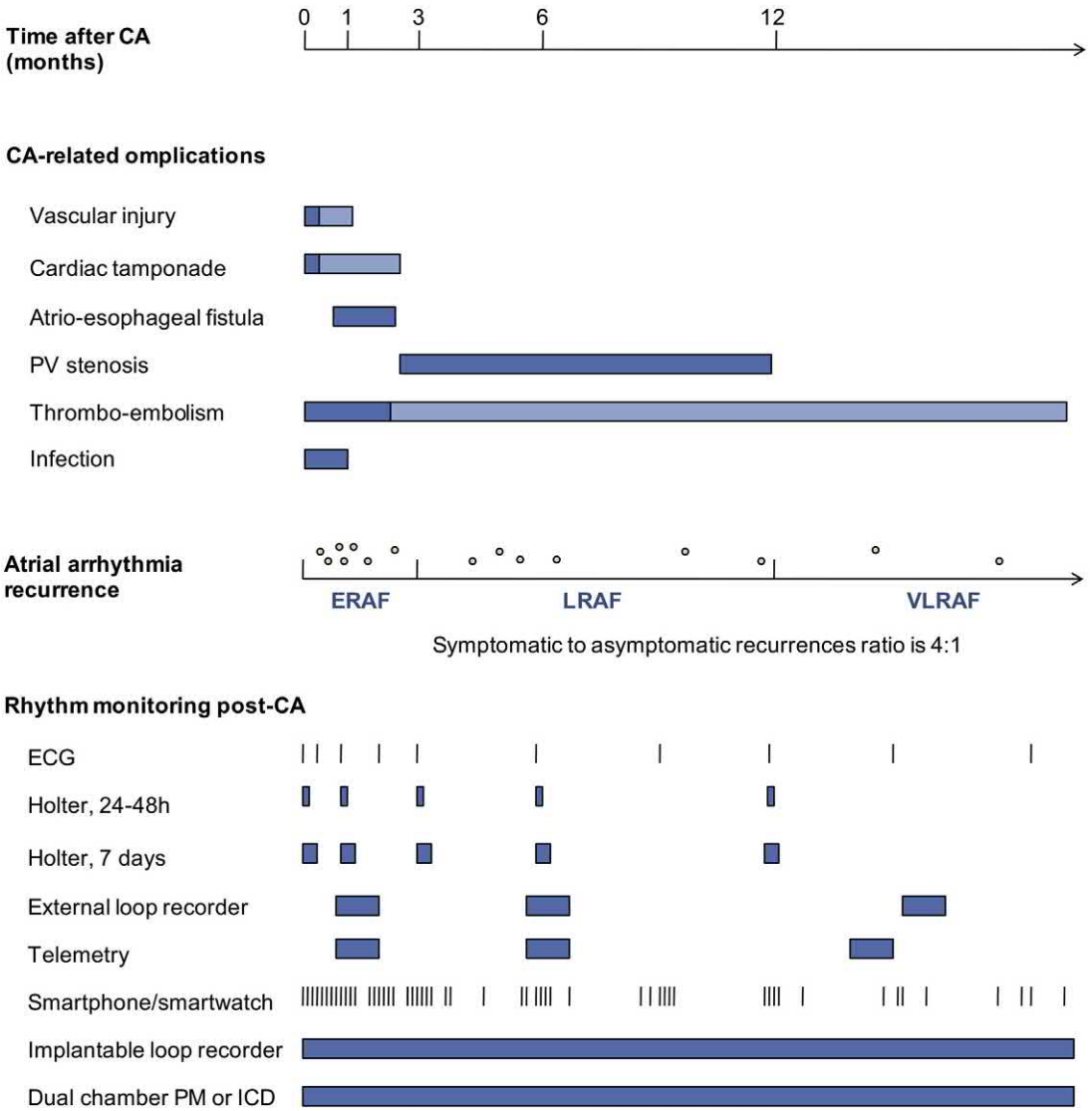

FIGURE 46.2 Timeframe of early and late complication occurrence following CA of atrial fibrillation (upper panel) and rhythm monitoring strategy after ablation procedure (lower panel). *CA*, catheter ablation; *ECG*, electrocardiogram; *ERAF*, early recurrence of atrial fibrillation; *ICD*, implantable cardioverter-defibrillator; *LRAF*, late recurrence of atrial fibrillation; *PM*, pacemaker; *PV*, pulmonary vein; *VLRAF*, very late recurrence of atrial fibrillation.

derived more specifically for predicting very late arrhythmia recurrences occurring >12 months after CA, identified male sex as an independent predictor of long-term procedure failure [32,44].

A generally less favorable rhythm outcome after CA in females could be significantly related to baseline differences in comparison to males [4,10,16,21,40,45]. At the time of ablation females are typically older and more often present with nonparoxysmal AF and a longer history of AF, see Table 46.1 and Fig. 46.1 [4,21,45]. Female patients also have more advanced atrial fibrosis and a higher index of LA size [16]. In addition, females have failed a higher number of antiarrhythmic drugs before referral to CA and more commonly experienced side effects of amiodarone [21,45]. The risk factors for AF progression and recurrence, such as hypertension, obesity, valvular heart disease, diabetes mellitus, diastolic heart failure, congestive heart failure, and chronic pulmonary disease, are also more prevalent among females than among males [4,10,21]. Sex-related differences in the recurrence rates among younger, otherwise healthy female patients may be explained by significantly higher parasympathetic tone in young females than in the age-matched males [39,40]. At the procedure, non-PV foci of AF were more frequently found in females compared to males [21]. It was reported that prevalence of arrhythmia triggers in superior vena cava was higher in females than in

males and that routine isolation of superior vena cava beyond PV isolation may significantly improve arrhythmia outcome particularly in females with paroxysmal AF [36,46].

Sex-related differences in rhythm outcome after multiple procedures

A final outcome after repeat CA is less favorable in females than in males as illustrated in Fig. 46.1 [10,36,39]. In females with the arrhythmia recurrence after index CA, a further rhythm control strategy is underutilized. Despite having a lower freedom from AF rehospitalization during the first year after CA (68.1% vs. 73.1%), females were less likely to undergo a cardioversion for AF relapse (17.1% vs. 21.4%) than male patients with the recurrence [10]. Moreover, females with the recurrence have significantly fewer repeat CA procedures than males (13.1% vs. 14.7%) [10,45]. The higher risk of complications [3,5,6], more advanced atrial disease [16,20], better response to antiarrhythmic drugs after CA [36], less symptomatic arrhythmia recurrences, as well as the patient preferences to continue only with medical treatment and refuse repeat invasive procedure [36] may influence the clinical decision-making to choose a more conservative treatment strategy in females than in males with AF relapse [45]. Finally, it seems that repeat CA procedure provides a considerably lower incremental benefit for long-term sinus rhythm control in females compared to males [39]. Thus, the 2-year arrhythmia recurrence rate after the second CA procedure was significantly higher among females than among male patients (50% vs. 28.2%) [39].

Therefore, clinicians should improve communication with their female AF patients in order to increase their motivation for invasive treatment of AF, which would ensure early referral to CA and better long-term procedure outcome [10,36].

Stroke and heart failure after ablation of atrial fibrillation

Delaying the CA procedure in females results in accumulation of cardiovascular comorbidities and increase in AF burden [4,10,21], which potentially increases the risk of systemic thromboembolism and heart failure [47,48]. The prevalence of risk factors for AF and/or heart failure, such as older age, diabetes mellitus, and hypertension, is significantly higher among females (vs. males) undergoing CA of AF [4,10,21]. Consequently, female patients who are referred to CA of AF are more likely to have the history of previous stroke and heart failure with preserved ejection fraction as well as a higher CHA_2DS_2-VASc score and nonparoxysmal type of AF compared with males [4,10,21,45]. These patient characteristics may substantially affect the long-term clinical outcome after AF CA [16,21,27,29,30,33–35,41,42,45].

Randomized studies showed no benefits of CA over antiarrhythmic drugs in younger AF patients with low prevalence of structural heart disease in respect to subsequent risk of death, stroke, and heart failure [49,50]. Therefore, the current expert consensus on catheter and surgical ablation of AF propose long-term oral anticoagulation therapy after CA in all patients with high inherent thromboembolic risk (i.e., CHA_2DS_2-VASc score of 2 or higher) irrespective of the postprocedure long-term rhythm outcome [12]. However, several nonrandomized retrospective studies including "sicker and older" AF population suggested significantly lower mortality (3%–6% vs. 7%–14%) and stroke rates (2%–3% vs. 4%–9%) with CA of AF than with further antiarrhythmic drug use [27]. Recently, a randomized multicentre study confirmed better 5-year overall survival (86.6% vs. 75%), cardiovascular survival (88.8% vs. 77.7%), and more substantial recovery of left ventricular ejection fraction (the median absolute increase of 8% vs. 0.2%) with CA versus conventional medical therapy in patients with AF and systolic left ventricular dysfunction, which are probably driven by more effective AF burden reduction following invasive treatment [25].

Available data indicate a similar death rate in the following year after CA of AF in both sexes, but a 38% higher risk of hospitalizations due to congestive heart failure and a 37% lower risk of admissions due to myocardial infarction in females than in males [10]. In addition, it seems that specific oral anticoagulant regimens may be associated with sex-related differences in thromboembolic events rate after CA [51]. For example, CA was associated with significantly lower risk of subsequent stroke than antiarrhythmic drugs among male patients (vs. females) using non–vitamin K oral anticoagulants (NOACs; HR 0.73), but no sex-related differences in the thromboembolic events rates were reported among patients treated with warfarin [51].

A single-centre retrospective analysis recently reported a low stroke rate of 1.5% during 18-month median follow-up after CA of paroxysmal AF [52]. According to the institutional strategy, oral anticoagulation was discontinued 3–6 months after CA in low-risk patients (i.e., in those with $CHADS_2$ score less than 2) [52]. Although thromboembolic events were clustered within the early weeks following CA procedure, the late events after AF ablation also occurred. In addition, investigators reported sex-specific predictors of stroke after CA. Thus, the baseline left ventricular ejection fraction % (HR 0.95) and the CHA_2DS_2-VASc score (HR 1.52) were independently associated with subsequent stroke risk after CA in females,

while the thromboembolic risk scores, such as CHA_2DS_2-VASc (HR 1.42), $CHADS_2$ (HR 1.65) and R_2-$CHADS_2$ (HR 1.76), and renal dysfunction (i.e., estimated glomerular filtration rate of <60 mL/min/1.73 m^2; HR 3.95), were multivariate predictors of thromboembolism post-CA in males [52].

The quality of life and symptomatic status after ablation of atrial fibrillation

It is estimated that more than a half of patients with AF experience symptoms attributable to the arrhythmia [53]. Symptom burden is higher among young patients with paroxysmal AF than among older patients with non-paroxysmal AF [12,53,54]. In addition, many AF patients also suffer from depression or anxiety, which may be related to symptom severity or the awareness of cardiac rhythm disorder [55]. These symptoms are often exacerbated during physical activity, potentially reducing exercise tolerance and quality of life (QoL) [53].

The rhythm control strategy using antiarrhythmic drugs offers a better improvement of symptomatic and functional status in patient with AF than the rate control strategy [12,28,54]. In addition, among symptomatic AF patients managed with a rhythm control strategy, CA is superior to antiarrhythmic drugs for the long-term QoL recovery [28]. Longitudinal studies with continuous rhythm monitoring by implanted loop recorders showed substantial conversion of symptomatic to asymptomatic AF episodes after CA, probably due to reduction of arrhythmia burden and cardiac denervation postprocedure [56].

The studies demonstrated that females with AF scored significantly lower QoL measures (Heart Survey SF 36 questionnaire), particularly the physical component score, than males [57]. Nevertheless, females are referred to CA of AF 3-times less and significantly later than males [4,10,21,26,35,36,45,54]. There are several possible explanations for this marked underrepresentation of females in CA population. First, there are concerns regarding higher major complication rates of CA and lower expected procedure efficacy in females than in male patients [3–5,10,27,36,45]. Second, symptoms due to unrecognized AF are more often ascribed to anxiety and psychiatric disorders in females. Finally, tolerance to AF symptoms could be simply higher in females and may be related to social discrimination of women in less developed communities [55].

However, it seems that symptomatic females experience less QoL improvement after CA of AF than males [54]. The study reported an inverse relationship between the level of daily activity and the AF burden after CA [58]. In patients with the relapse after the procedure, daily activity becomes limited when the daily AF burden exceeds 500 min and becomes considerably reduced after 1000 min of the arrhythmia. Among other clinical factors, such as AF-related symptoms, age, hypertension, and heart rate variability, the patient sex significantly affects the association between daily activity and AF burden following CA [58]. Thus, a lower daily AF burden more substantially influences the level of usual physical activity in females than in male patients who underwent CA procedure [58].

Follow-up strategy after ablation of atrial fibrillation

All patients who underwent CA of AF should be seen in follow-up regularly after the procedure in order to (1) identify complications, (2) detect recurrence of atrial arrhythmias, and (3) appropriately adjust long-term antiarrhythmic and anticoagulation drug therapy according to clinical outcome after CA. Since procedure-related complication occurrence and arrhythmia recurrences demonstrated the sex-related differences (Fig. 46.1), a closer early follow-up strategy in females may be considered.

Monitoring of complication postprocedure. Fig. 46.2 illustrates the timeframe of major complication occurrence following CA of AF. In the first month after CA, it is important to recognize and promptly manage "early" complications (e.g., infections, vascular injury and bleeding, delayed cardiac tamponade and pericarditis, atrioesophageal fistula, and thromboembolic events), and therefore the first visit should be scheduled after 2–4 weeks after discharge [3,5,10,21,45,52]. Further follow-up consisting of visits at 3, 6, and 12 months following CA is recommended for assessment of late complications, such as symptomatic PV stenosis or systemic thromboembolism [27,28,52].

Monitoring of rhythm postablation. Early recurrence of atrial arrhythmia within the 3-month blanking period is common and routine use of antiarrhythmic drugs in the first weeks following CA is reported to significantly supress readmissions for early cardioversions [18,27,28]. Clinical decision on the use of antiarrhythmic drugs beyond blanking period is based on the initial result of CA (e.g., incomplete PV isolation, termination of AF by electrical cardioversion and not by ablation, findings of extensive low-voltage areas within the LA or complex anatomy at CA procedure, history of multiple CA procedures, etc.) as well as the individual patient characteristics that may influence long-term rhythm outcome (e.g., large LA, advanced age, nonparoxysmal type of AF and/or multiple comorbidities at baseline, etc.) [18,27,28]. Since arrhythmia recurrences are most common within the first 6–12 months after CA, it is suggested that rhythm

monitoring should be more intense during the first post-CA year followed by further regular annual clinical check-ups, as illustrated in Fig. 46.2 [18,54].

Fig. 46.2 shows various modalities of rhythm monitoring commonly used after CA procedure. Continuous monitoring by an implantable loop recorder or pacemaker/implantable cardioverted defibrillator with an atrial electrode provides reliable long-term detection (for several months to years) of arrhythmia recurrence even in asymptomatic patients with very high sensitivity of 98% [27,28,56]. Moreover, a recent study comparing implanted loop recorder and 24 h Holter for rhythm monitoring after CA of AF indicates an almost sevenfold underestimation of AF recurrence rate by intermittent monitoring and significant increase of the ratio of asymptomatic to symptomatic AF episodes from 1.1 before to 3.7 after the procedure [59]. Importantly, a continuous monitoring specifically enables assessment of residual arrhythmia burden after CA which is recently reported to correlate with clinical endpoints such as all-cause and cardiovascular mortality, progression of systolic heart failure, risk of cryptogenic stroke, and QoL postprocedure [22,25,50]. However, continuous monitoring strategy is invasive, expensive, and in routine clinical practice is reserved only for patients with other indications for device implantation [18].

Hence, a routine rhythm follow-up strategy after CA of AF mostly consists of intermittent rhythm monitoring by simple, noninvasive, and easily available tools, such as serial 24 h, 48 h, or 7 days Holter recordings, or repeated use of transtelephonic transmission systems, external loop recorders, or telemetry (up to 1 month), all of them showing only moderate sensitivity for AF detection between 30% and 70% [18,27,28,54]. Although smartphone and smartwatch recently demonstrated a high sensitivity for AF detection of 97% thus offering an attractive option for noninvasive rhythm assessment, there is yet no consensus on their widespread use for post-CA monitoring [60]. Most of these noninvasive tools rely on patient's symptoms and depend on patient adherence. In addition, short-lasting, sporadic, and asymptomatic arrhythmia episodes may remain undetected using only intermittent monitoring [18].

Conclusions

Females with AF are less likely to be referred to the index as well as a redo CA procedure compared to males. Generally, females referred for CA of AF are older, "sicker," and have a longer history of AF (Fig. 46.1). Female sex is not only a risk factor for acute and late procedure-related complications but also is associated with less favorable long-term rhythm outcome after CA. In order to improve CA outcome in females, a physician should encourage female patients to undergo CA procedure earlier in the course of their AF, preferably in an experienced electrophysiology center. In addition, females who underwent a CA of AF could need a more intense follow-up and rhythm monitoring strategy to ensure timely detection and management of early and late complication postprocedure as well as the late atrial arrhythmia recurrence, and the follow-up schedule should be outlined at discharge.

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Chapter 47

Sex differences in atrial fibrillation: focus on thromboembolic risk and anticoagulation therapy

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Introduction

The prevalence of atrial fibrillation (AF) continues to rise globally both in men and women. Furthermore, there is an ample amount of evidence to indicate that it affects the two sexes differently, with the age-adjusted incidence and prevalence lower in women (Fig. 47.1) [1,2]. Indeed, men are more susceptible to AF but as women live longer and increasing age is an independent risk factor for AF, the lifetime risk of developing this condition is equivalent and approximately 30% for both sexes [3,4].

In addition to the epidemiology, there are also variations in the symptomatology between men and women. In the multicenter Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) cohort, women with AF were noted to have more symptoms, a greater degree of functional impairment, and a poorer quality of life. In the study, differences were also noted in the management of AF between the groups. Women were less likely to have cardioversion or AF ablation but more likely to undergo atrioventricular nodal ablation compared with men. After a median follow-up period of 2.3 years, females had a lower adjusted risk of all-cause mortality but higher risk of stroke and non−central nervous system embolism compared with men, meaning the disease burden was greater for women [5].

Other notable differences have also been observed in the risk factors for thromboembolism and outcomes following stroke. In terms of risk factors, women are more likely to have heart failure and hypertension but there are no significant differences between the prevalence of other comorbidities such as diabetes mellitus and chronic kidney disease [6]. Following a stroke, women are more likely to suffer from a significant physical impairment, leading to limitations on activities of daily living that impact their quality of life [7].

There is much to discuss about the sex differences in the epidemiology, risk factors, disease progression, complications, and management of AF, but this chapter explores differences in the AF-related thromboembolic risk between males and females and their implications on oral anticoagulation therapy (OAC) (Fig. 47.1).

Is there a difference in the thromboembolic risk?

The presence of AF is associated with a fivefold increase in the risk of stroke and thromboembolism. However, this increase is not homogenous. A higher risk of stroke in women with AF has been observed in historical trials and later replicated in observational cohort studies [8−10]. In a recent systematic review and metaanalysis, Marzona and colleagues [11] looked at 40 studies to explore the sex differences in stroke and thromboembolism between males and females. They noted that females had a 24% increase in the relative risk of stroke but no differences were found in other thromboembolic events, major bleeding, and all-cause mortality between the groups. These findings, in part, justify the inclusion of female sex in risk stratification tools such as CHA_2DS_2-VASc score.

Interestingly, the increased risk of stroke in females is dependent upon age and presence of other risk factors (Fig. 47.2), i.e., excess stroke events have not been observed in females with AF who are <65 years without other risk factors for stroke [10,12]. Thus, the concept of

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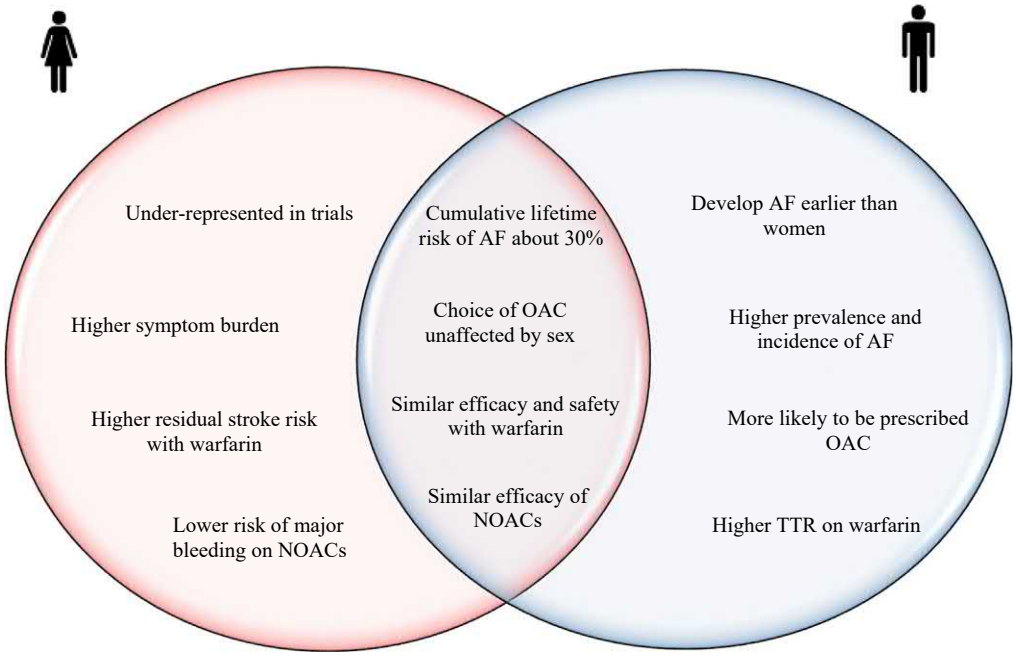

FIGURE 47.1 Some similarities and differences between males and females with atrial fibrillation. *AF*, atrial fibrillation; *BMI*, body mass index; *NOACs*, novel oral anticoagulants; *OAC*, oral anticoagulants; *TTR*, time in therapeutic range.

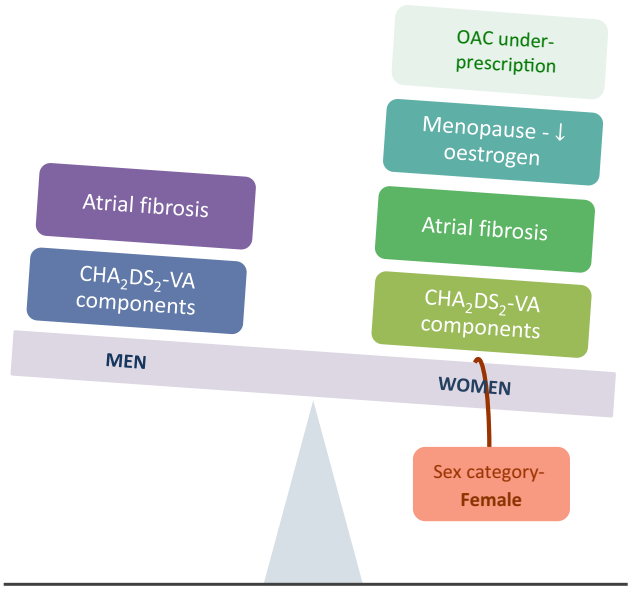

FIGURE 47.2 Factors contributing to the thromboembolic risk in men and women with atrial fibrillation. CHA_2DS_2-VA components — *C*, Congestive cardiac failure; *A*, age (65—74 years); *A*, age (≥75 years); *D*, diabetes mellitus; *H*, hypertension; *S*, previous stroke/TIA/systemic embolism; *V*, vascular disease.

female sex as a stroke "risk modifier" rather than a risk factor was evolved. Consequently, the CHA_2DS_2-VA score (i.e., exclusion of the sex [Sc] component) has been explored as an alternative to the CHA_2DS_2-VASc score in recent years. The latest Australian guidelines for AF recommend using the sexless CHA_2DS_2-VA score for predicting stroke risk in AF, on the basis that being female alone does not sufficiently or consistently confer an additional stroke risk [13]. However, this has been challenged by the scientific community, as exclusion of sex from this equation could lead to underestimation of the stroke risk and underprescription of OAC in females [14].

In a study by Nielsen and colleagues [15], the CHA_2DS_2-VA score was retrospectively applied to nonvalvular AF patients who had not been commenced on OAC therapy yet and the rates of thromboembolism were calculated (Fig. 47.3). The study indicated that women had a higher mean CHA_2DS_2-VA score, 1-year thromboembolic event rate, and higher stroke risk compared with men across all scores, apart from 0 and 3. In the 5-year follow-up analysis, women exhibited a 23% higher risk than men with the same CHA_2DS_2-VA score, for scores between 1 and 5. The study confirmed that female sex is indeed a prognosticator for AF-related stroke. However, it made less of a difference toward the decision on whether or not to anticoagulate an individual, as the excess risk in women was observed only among patients who already had an indication for OAC, due to presence of additional CHA_2DS_2-VA score risk components. Nonetheless, the authors noted that specific components in the CHA_2DS_2-VASc score may influence the stroke risk/rates differently, and given that sex appears to modify this risk (in the presence of other factors), the study did not recommend a change to the modified CHA_2DS_2-VA score. In addition, exclusion of sex from the score may not only confuse the clinicians but also unintentionally indicate that women carry less stroke risk than men.

Regardless of the scoring system used to define the impact of sex on thromboembolic risk, it is apparent that there is indeed a difference between the sexes. Women are at a higher risk of stroke and less likely to have favorable outcomes following this complication, differences which are not wholly explicable at present.

What causes the sex difference?

Women develop AF at an older age. In the Framingham Heart study, 74% of women with AF were ≥70 years while only 58% of men accounted for this age group. As older individuals are likely to have more comorbidities, the study strongly suggested that the increased number of comorbidities is possibly causative of AF in women [2].

Comorbidities that are risk factors for AF are numerous, but only few account for differences between the sexes. Existing literature indicates that heart failure (odds ratio [OR] 4.5 in men; 5.9 in women) and valvular heart disease (OR 1.8 in men; 3.4 in women) increase the risk of AF to varying degrees for both sexes, while the impact of diabetes mellitus, obesity, and myocardial ischemia are similar in men and women [16]. This alone signifies that there are distinctions in the pathophysiology of AF between men and women.

Currently, AF is thought to originate in the pulmonary veins because of triggered activity and micro reentry (Fig. 47.4). Once initiated, the abnormal rhythm is maintained because of electrical heterogeneity of the myocardium and structural remodeling. AF in turn can promote further electrical and structural remodeling that promotes further AF [17,18]. Although this mechanism is observed in both sexes, it does not sufficiently explain the differences in presentation, symptomatology, and prognosis of AF between sexes. Body mass index (BMI), structural differences, genetics, and hormones have all been proposed as possible reasons.

Obesity, defined by elevated BMI of ≥30 kg/m^2, is thought to be an independent predictor of AF. Data from a Norwegian longitudinal population-based study demonstrated that high BMI increased the risk of developing AF in both sexes, independent of age, blood pressure, smoking, and other typical risk factors for AF. This association was the strongest in men, specifically <65 years of age. Although the reasoning behind this is yet to be fully elucidated, obesity-induced cardiac remodeling in the form of fibrosis may explain the difference [19].

Structurally, the myocardium differs between the sexes. Men have a larger left atrium and increased ventricular wall thickness compared with women. Both are associated with an increased risk of AF, partly explaining its higher prevalence among men [20]. However, once a diagnosis of AF has been established, advancing age and female sex are associated a higher burden of atrial fibrosis. The resulting advanced fibrosis which contributes to thrombus formation may explain the increased stroke risk in women [21].

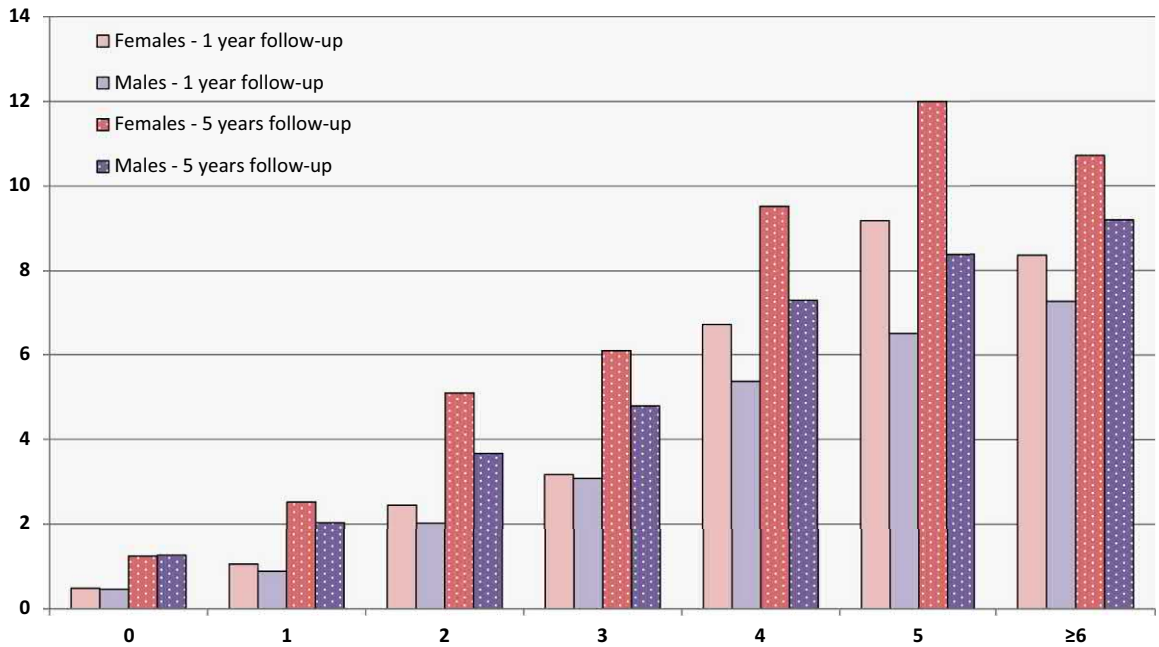

FIGURE 47.3 The graph demonstrates the absolute risks of thromboembolism across the CHA_2DS_2-VA scores for females and males at 1 and 5 years of follow-up. *With permission from Nielsen, Skjoth, Overvad, Larsen, Lip. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA score rather than CHA2DS2-VASc? Circulation 2018;137(8):832–40.*

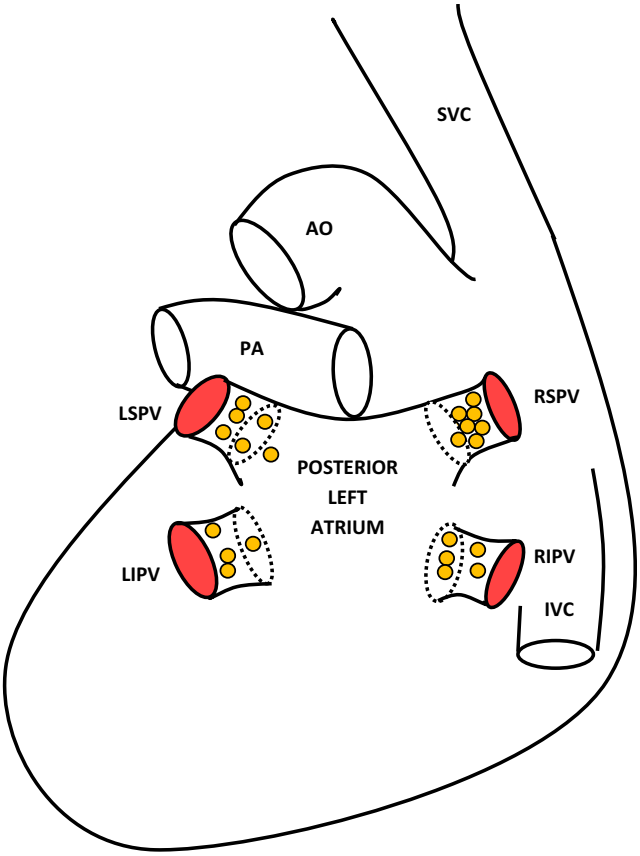

FIGURE 47.4 A sleeve of myocardium extends between the left atrium and pulmonary veins which contain multiple AF triggering foci. *AO*, aorta; *IVC*, inferior vena cava; *LIPV*, left inferior pulmonary vein; *LSPV*, left superior pulmonary vein; *PA*, pulmonary artery; *RIPV*, right inferior pulmonary vein; *RSPV*, right superior pulmonary vein; *SVC*, superior vena cava.

One biological explanation for the increased stroke risk in females relates to sex hormones. Decreased levels of estrogen and other postmenopausal hormonal changes have been attributed to the increased incidence of AF in women over the age of 50 years, owing to the increase in risk factors for AF such as blood pressure, BMI, and cholesterol as a result of reduced estrogen levels [22]. This is further supported by the higher incidence of AF in patients taking antiestrogen therapy compared with those taking estrogen-based hormone replacement therapy, although evidence suggesting otherwise also exists [23].

The expression of estrogen and androgen receptors in cardiac myocytes suggests that these hormones likely have a direct influence on electrophysiological processes and hence the propensity for AF development. Animal studies have demonstrated that both estrogen and testosterone regulate various ion channels and lead to alterations in ion currents. The estrogen-induced prolongation of the action potential duration is believed to have an antiarrhythmic effect, while its modulation of certain channels, which are prevalent in pulmonary veins and appear to have a role in AF maintenance, may potentially affect triggered activity that provokes AF. Furthermore, estrogen has also been shown to increase triggered activity by affecting calcium currents [24].

For men in contrast, triggered activity is reduced by testosterone and low levels of this hormone have been associated with an increased risk of AF. In an analysis of the Framingham Heart study, each 1-standard deviation (SD) reduction in testosterone was associated with a 1.5-fold and 3.5-fold increased risk of AF for men between 55 and 69 years and over ≥80 years, respectively. The association was observed but did not reach statistical significance in those aged 70−79 years. This was thought to be due to the high competing risk of mortality from multimorbidities in this age group, attenuating the association between reduced testosterone and AF. Low levels of testosterone have been associated with the development of other risk factors for AF such as hypertension, dyslipidemia, and obesity, with the latter also linked to adverse atrial electrical remodeling [25]. Interestingly, normalization of testosterone levels following testosterone replacement therapy has been associated with a significantly lower incidence of AF in men in a retrospective observational study, but these findings are yet to be validated in a clinical trial [24,26].

The current evidence base also includes smaller-scale studies with conflicting results, where higher levels of testosterone have been associated with AF development in men and a greater number of arrhythmic episodes compared to the placebo group [24,27,28]. Hence, further studies need to be conducted to fully explore this relationship.

Should anticoagulation practices be different?

Current guidelines

Both the European Society of Cardiology (ESC) and American AF guidelines recommend using the CHA_2DS_2-VASc score for stroke risk stratification and guiding anticoagulation decisions [29,30,31]. According to the ESC guidelines, the presence of one CHA_2DS_2-VASc risk factor (apart from female sex) is enough to considerably increase the risk of stroke, meaning a score of ≥1 in men and ≥2 in females should warrant anticoagulation for patients with AF. As previously established, female sex alone does not increase the risk of stroke in the absence of other risk factors. In the American guidelines, treatment is recommended for scores ≥2 and ≥3 for men and women, respectively. For patients with one non-sex CHA_2DS_2-VASc risk factor, OAC may be considered.

As alluded to previously, new guidelines were introduced in Australia in 2018, adopting the sexless CHA_2DS_2-VA score to assess AF-related stroke risk. Anticoagulation is indicated if the score is ≥2, with non-

vitamin K oral antagonists (NOACs) recommended in preference to warfarin. Although this deviation from international guidelines was met with some scrutiny from the medical community, the authors felt that inclusion of the female sex category in the stroke risk stratification tool had no added value and it continues to be used [32].

Oral anticoagulation therapy prescription

Despite OAC therapy being the mainstay of treatment for stroke prevention, its underuse remains a major concern and several studies have been undertaken to delineate any sex differences in OAC prescription rates (Fig. 47.5).

In a French study, two factors were significantly associated with vitamin K antagonist (VKA) underprescription, concurrent NSAID use, and female sex. This was true regardless of the level of stroke risk [33]. Similarly, data from the national PINNACLE Registry in the United States also demonstrated that women were significantly less likely to receive OAC at all levels of the CHA_2DS_2-VASc score and more likely to be prescribed aspirin, despite having a risk score of ≥ 2 [34]. These findings were consistent even after the widespread introduction and uptake of NOACs [35]. This is in contrast to the Euro Observational Research Program survey (EORP) which showed better OAC prescription rates in females compared with males and the Global Anticoagulant Registry in the FIELD (GARFIELD) registry, where no significant sex differences in OAC use were found [6,36].

In addition to the above, studies also suggest that women are less likely to be on the correct guideline-recommended dose and more susceptible to under- or overdosing [37].

Oral anticoagulation therapy use

Aside from the issue of OAC underprescription in women, studies have focused on identifying whether there are any disparities in the degree of anticoagulation between the two sexes. While NOACs are increasingly being utilized, the measure of their anticoagulant activity is far more difficult to determine compared with VKAs, where the degree of anticoagulation control is represented by the time in therapeutic range (TTR). Indeed, the efficacy of VKAs is dependent upon the TTR, with a higher TTR offering better protection against the stroke/bleeding risk. Female sex has been associated with an increased likelihood of poorer International Normalised Ratio (INR) control and lower TTRs, reflective of poorer compliance and sex disparities in care. Clinical inertia has also been proposed as an element contributing to this, possibly because of females being more vulnerable because of their older age [38,39].

In recognition of this, female sex is included in the SAMe-TT_2R_2 score which is used to predict patients who are unlikely to do well on VKAs such as warfarin. Those with a score of 0−1 are predicted to do well, whereas a score of ≥ 2 increases the probability of a suboptimal TTR. Clinicians must therefore consider this before initiation of

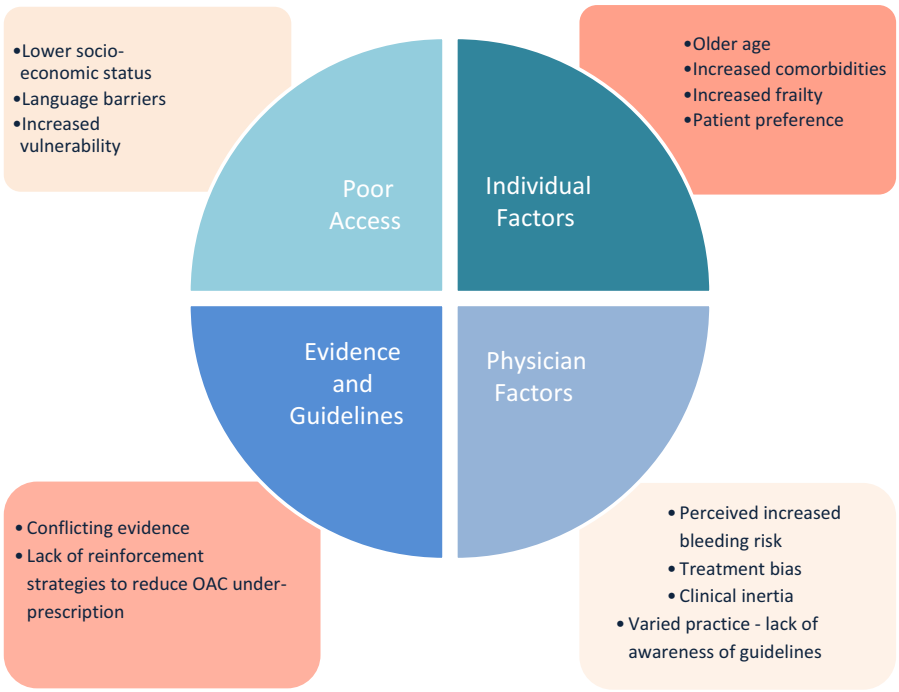

FIGURE 47.5 Factors which contribute to OAC underprescription in females. *OAC*, oral anticoagulation.

warfarin or another VKA. If a female patient has other factors that could indicate poor TTR such as smoking and interacting medications, alternatives such as NOACs should be considered [40]. With the shift in practice and increase in the uptake of NOACs in preference to VKAs, suboptimal TTRs are anticipated to be less of an issue unless NOACs are contraindicated (e.g., in valvular AF).

Oral anticoagulation therapy effects

Warfarin is a well-established VKA that has been used for stroke prevention in AF for decades. In a pooled analysis of randomized controlled trials (RCTs) comparing warfarin versus placebo, the decrease in stroke risk was similar in both sexes [8]. Moreover, no sex-specific differences have been observed in terms of major bleeding [41,42].

Although this may be the case, women treated with warfarin have a 28%–54% higher residual thromboembolic risk than men [43,44]. Given that TTR is a predictor of clinical outcomes, it is possible that the higher residual stroke risk in women is partly because of poor TTR control on warfarin [43,45–47]. Nonetheless, the AFFIRM study was key in demonstrating that a lower TTR only partially explains this, as the increased stroke risk in women was still high after adjustments were made for this factor. One explanation for this could be the sex-specific variations in the pharmacodynamics of warfarin, which may necessitate a higher INR threshold to observe a decrease in the stroke risk that is comparable to that of men. A target INR between 2 and 3 was defined on the basis of anticoagulation studies which included few women and presuming that anticoagulants affected both sexes in the same way [43].

NOACs provide an alternative to warfarin as they do not require routine monitoring and are associated with fewer drug interactions. The efficacy and safety of NOACs (namely dabigatran, rivaroxaban, apixaban, and edoxaban) compared with warfarin have been established in their respective phase III trials [48–51]. Granted, these trials were underpowered to detect sex disparities particularly as females comprised $\leq$40% of the study participants but existing evidence does not suggest significant differences in the efficacy or the residual stroke risk between men and women.

In a pooled metaanalysis of these RCTs, NOACs reduced stroke and systemic embolic events by 19% and major bleeding by 14% compared with warfarin, irrespective of the sex [52]. Subgroup analysis did not reveal any differences between the sexes for these outcomes. In another metaanalysis, women treated with NOACs had significantly lower major bleeding compared with men [44,53].

It is possible that individual NOACs exert their effects differently on males and females because of variations in their pharmacokinetic and pharmacodynamic properties. Currently, there are no head-to-head comparisons between the different NOACs to accurately analyze sex variations on the efficacy and safety of these drugs. Subanalyses from the ROCKET-AF (rivaroxaban) and ARISTOTLE (apixaban) trials have shown a reduced risk of bleeding in women compared with men [54,55]. More recently, a network metaanalysis which was used to perform indirect comparisons provided evidence for sex differences in the safety of individual NOACs. For women, apixaban and edoxaban were associated with lower risks of major bleeding compared with other NOACs, while apixaban was also associated with significantly lower risks of major bleeding compared with rivaroxaban in men. The lower risk of major bleeding in women compared with men was unique to NOACs (and not warfarin) and was attributed to dose adjustments based on weight (women receiving smaller doses) and concomitant use of antiplatelets (men are more likely to be on antiplatelets) [53].

Controversially, data from this metaanalysis also reported higher risks of stroke and systemic embolism in women on NOACs compared with men (risk ratio 1.19; CI 1.04–1.35). However, this may be a reflection of the higher baseline stroke risk in women who were older with a higher $CHADS_2$ score. Furthermore, the increased stroke risk in women was also observed in the warfarin-treated arm, further suggesting that this is more likely to have been contributed to by the baseline stroke risk factors rather than the OAC agents.

The comparable efficacy and lower risk of major bleeding certainly make NOACs a more attractive choice for women.

Future practice

Whether due to older age, frailty, a perceived increased bleeding risk, or presence of other factors, it is evident that women are treated far more conservatively compared with their male counterparts. This is true for OAC therapy to minimize the prospect of thromboembolic phenomena as well as attempts to restore sinus rhythm with either cardioversion or catheter ablation, despite the higher risk of stroke, debilitating symptoms, and poorer quality of life in women. While there may be sex-specific attributions to these differences, current practice in part is likely contributing to this, necessitating a more conscientious and proactive approach to the management of AF in women (Fig. 47.6).

Given that treatment with NOACs eliminates the higher residual stroke risk seen with warfarin and is safer for women in terms of the major bleeding risk, their net clinical benefit is much higher and it may be prudent to offer these drugs at first instance, in preference to VKAs. Easy reversibility with vitamin K has been one of the few areas

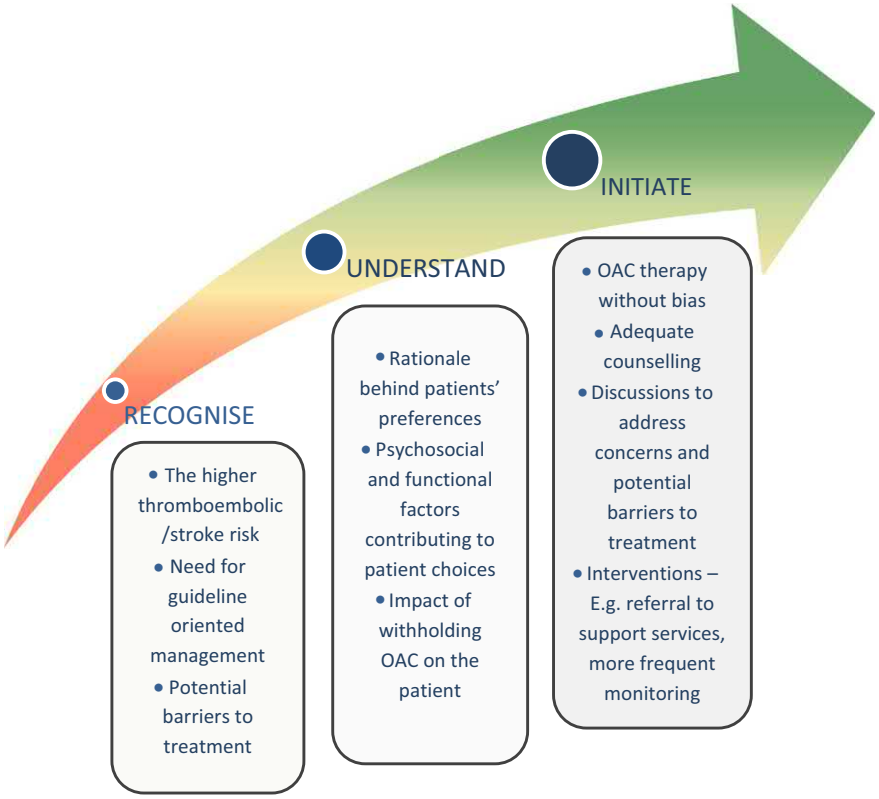

FIGURE 47.6 Steps that can be taken by physicians to improve OAC prescription rates and treatment adherence in females. *OAC*, oral anticoagulation.

where warfarin has shown superiority over the NOACs but with the recent availability of andexanet alfa as an antidote for the factor Xa inhibitors alongside idarucizumab (for dabigatran), NOACs continue to rise in favor [56,57]. Indeed, the patients' views and their individual risk profile play an important role in determining the drug of choice and providing personalized treatment.

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Chapter 48

Sex and cardiac electrophysiology

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A majority (>60%) of atrial fibrillation (AF) patients have at least mild symptoms that can be related to their arrhythmia, and a substantial portion (17%) even suffer from severe or disabling symptoms, according to large observational community−based registries such as the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF) [1]. The large proportion of symptomatic patients is also supported by the prospective, real-world registry, The PREvention oF thromboembolic events—European Registry (PREFER in AF) in which only a minority (8.1%) of patients were asymptomatic as evaluated with European Heart Rhythm Association (EHRA) scores [2,3]. Similar findings were reported by the Euro Heart Survey, with available follow-up data regarding symptoms status from 182 hospitals in 35 different European countries, in which 68% of 3607 consecutive AF patients reported symptoms at the baseline visit [4]. These findings are, however, in sharp contrast to observations made in the EORP-AF Pilot Registry, which reported a high prevalence (almost 40%) of asymptomatic AF patients, enrolled based on presentation to cardiology clinics [5]. The higher prevalence of asymptomatic patients in that registry may, however, be explained by their high proportion of permanent AF patients. The EHRA symptom scale (Table 48.1) is a scoring system for AF-related symptoms and, as the New York Heart Association classification for heart failure, it reflects physicians' perspectives of patients' health status and is recommended as a simple and valuable tool to assess symptom severity and impairments in daily activities guiding treatment decisions and conducting research in AF patients [6]. Several trials have used the EHRA symptom scale (Table 48.2) to assess how symptoms, including palpitations, fatigue, dizziness, dyspnea, chest pain, and anxiety, during AF affect the daily activity, ranging from none to symptom frequency or severity that leads to a discontinuation of daily activities (Table 48.1). An evaluation of the severity of symptoms using the EHRA symptoms scale in AF patients included in the ORBIT-AF registry showed that 34% had no symptoms (EHRA class I), while 48% had mild symptoms not affecting normal daily activity, 16% had severe symptoms affecting normal daily activity, and 2% had disabling symptoms requiring a discontinuation of normal daily activity (EHRA classes II−IV, respectively) [7]. In the registry, there were 10% of patients with first-detected AF; 48% with paroxysmal AF, 15% with persistent AF, and 28% with permanent AF [7]. The most frequently reported symptoms when using the EHRA classification system are fatigue, palpitations, and dyspnea (Fig. 48.1) [3].

Patients with paroxysmal AF report in general more symptoms (80%) than patients with persistent (76%) and permanent AF (51%) (Fig. 48.2) [8]. This may be related to the observation that patients with paroxysmal AF more frequently suffer from palpitations than persistent AF, and a symptom such as palpitations is likely easier to be recognized as being AF related than other more diffuse symptoms. Paroxysmal AF patients have been shown to more often suffer from palpitations, dizziness, and chest pain, whereas nonparoxysmal AF patients complain of dyspnea, fatigue, and effort intolerance, according to data from the prospective, observational, multicenter cohort registry, the Basel Atrial Fibrillation Cohort with 1553 patients with documented AF (Fig. 48.2) [8].

Symptoms and quality of life (QoL) also depend on sex and gender. Women with AF have a substantially higher (68%−95%) symptom burden and a lower health perception (58%−90%) than men (Fig. 48.2) [8−11]. They more frequently report palpitations, lightheadedness/dizziness, and fear/anxiety [9,10] and are also reported to have a greater functional impairment with a higher proportion classified in EHRA class III and IV, as compared with men [9,10]. Another study with new-onset AF and normal echocardiogram also reported that women more often had palpitations, fatigue, and chest pain [12]. Although several factors including older age and more frequent paroxysmal

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TABLE 48.1 The European Heart Rhythm Association symptom scale.

EHRA class	Classification of AF-related symptoms
I	No **symptoms**
II	Mild **symptoms** = normal daily activity not affected
III	Severe **symptoms** = normal daily activity affected
IV	Disabling **symptoms** = normal daily activity discontinued

Six symptoms, including palpitations, fatigue, dizziness, dyspnea, chest pain, and anxiety, during atrial fibrillation are evaluated with regard to how it affects the daily activity, ranging from none to symptom frequency or severity that leads to a discontinuation of daily activities. Validation studies showed moderate correlations with quality of life (QoL) questionnaires including the Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire [1,6] the standardized health status questionnaire (EQ-5D-5L), and the Perception of Anti-Coagulant Treatment Questionnaire (PACT-Q) questionnaire [3]. It does not, however, consider other symptom dimensions such as anxiety, treatment concerns, and ongoing or anticipated adverse effects of medication, some of which are captured by general QoL scales [3]. Although the score itself had limited value in predicting outcome of AF interventions, its individual components were related to different and specific clinical events and may therefore be helpful to target patient management [3]. *AF,* atrial fibrillation; *EHRA,* European Heart Rhythm Association.

AF in female patients with AF as compared to male patients might explain the sex-related differences shown in several prior studies [9,10,12,13]. These sex-specific differences in AF-related symptoms persisted after multivariable adjustment in a more recent trial [8]. Given the knowledge that increased heart rate is an important predictor of symptoms [14], one cannot exclude that although the study adjusted for resting heart rate [8], women with paroxysmal AF may still have higher ambulatory heart rates, as previously described on Holter−ECG recordings in patients with paroxysmal AF [15]. Plausible mechanistic explanations may be decreased vagal tone and a greater prevalence of thyroid dysfunction in women [16].

QoL can be measured not only using validated and well-established scales such as the Medical Outcomes Study 36-item Short-Form health survey (SF-36) and the EuroQoL-5D (EQ5D) but also using more AF-specific scales (Table 48.2). The benefit with a generalized QoL scale is its wide usage in medicine enabling comparisons of health-related QoL between different disease states and QoL changes to be converted to cost-effectiveness measures by QALYs when using the EQ5D. The true advantage with AF-specific scales as compared to more generalized questionnaires is unclear and requires validation through randomized trials. Even though the majority of these questionnaires have been validated, very few have assessed the Clinically Important Difference [17−19]. Among AF-specific QoL questionnaires, The Atrial Fibrillation Effect on QualiTy of Life (AFEQT) score (Table 48.2) is one that correlated closely with symptom severity measured by the EHRA class, when using data from the ORBIT-AF registry [1].

As compared to the general population, AF patients have a worse health-related QoL and reduced exercise tolerance [1,8,20,21]. The AFEQT questionnaire score was found to be lowest among patients with new-onset/first-detected AF with scores of 76.9 (54.6−88.0), as compared with patients having paroxysmal AF with 83.3 scores (67.6−93.5), persistent AF with 80.1 scores (61.1−94.0), or permanent AF with 83.3 scores (68.5−93.5) AF ($P < .0001$) [7]. Female sex was shown to be an independent predictor for a lower health perception and QoL after controlling for baseline characteristics and all AF-related symptoms (OR, 0.76; 95% CI, 0.68−0.84) [8,9]. Apart from female sex, patients with the worst AF-related QoL were more likely younger and had more comorbid diseases [7]. Other patient factors associated with reduced QoL in AF patients were apart from new-onset AF also higher heart rate, obstructive sleep apnea, symptomatic heart failure [22], hypertension, chronic obstructive pulmonary disease [23], overweight [24], and coronary artery disease [7]. Although older patients had fewer symptoms and greater treatment satisfaction, the lack of association to daily activity scores made it difficult to adequately judge the effects on QoL [7].

Assessing the key drivers of symptoms and health-related QoL in AF patients is important when identifying an optimal treatment strategy. Although AF burden [25] and several comorbidities may be important determinants of health-related QoL, the complexity in finding the main contributors is illustrated by the observation that only psychological functioning consistently predicted both AF-related symptoms and QoL, while no clinical factors (left ventricular diastolic function, AF burden, ventricular rate during AF) were independent predictors [21]. Individuals with AF were more likely to develop anxiety disorder [26] and had a higher burden of depressive symptoms driven by somatic symptom dimensions [27]. Moreover, QoL was more impaired in AF patients with a distressed personality type (type D) [28].

An optimal management strategy for AF patients should confirm that existing symptoms are AF related and

TABLE 48.2 Quality of life and symptom questionnaires.

Questionnaires	Description QoL/symptoms	Used in trials and registries	Advantage	Disadvantage
SF-36; Short-Form Health Survey	QoL. Physical and mental components: eight equally weighted scores (0–100); vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health.	[42,45,47]	Validated in several disease states	Value for cost benefit trials unknown
EQ-5D; EuroQol Five Dimensions Questionnaire	QoL. Five health state measures: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Replies in 3 or 5 level scales. Overall health status evaluated by a visual analogue scale (EQ-VAS).	[45]	Quality-adjusted life years for cost utility analysis	
AF-specific questionnaire				
AFEQT; AF Effect on Quality of Life Survey	Questions: four on AF-related symptoms, eight on daily function, six on AF treatment. 7-point Likert scale.	[1,48]	Simple	Limited validation
AF-Qo; Quality of Life Questionnaire for Patients with AF	18 items on psychological, physical, sexual activity. 5-point Likert scale.	[36]	Simple	Limited validation; SF-36
SCL; Arrhythmia-Related Symptom Checklist	16 items; AF symptom frequency—severity.	[30,47,49]	Time consuming, applicability	Extensively validated, applicability
ASTA; Arrhythmia-Specific Questionnaire in Tachycardia and Arrhythmia	Number of AF episodes, average episode duration last 3 months. Eight symptoms, two disabling symptoms scored 1–4 each.	[50]	Simple, Validated with SCL, EQ5D, SF-36	One validation study
CCS SAF; Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale	Like EHRA scale. O = asymptomatic, I = AF symptoms minimal effect on patient's QOL, II = AF symptoms minor effect on patient QOL, III = symptoms moderate effect on patient QOL, IV = AF symptoms severe effect on patient QOL.	[51]	Simple, validated with SF-36, AFSS.	Poor correlation subjective AF burden; not so specific
AFSS; University of Toronto Atrial Fibrillation Severity Scale	10 items on frequency, duration, severity. 7-point Likert scale.	[42,47]	Time consuming, applicability	Validated, reproducible; applicability
MAFSI; Mayo AF-Specific Symptom Inventory	10 items on AF symptom frequency - severity. 5-point–3-point Likert scale.	[48]	Validated in AF ablation trials	Limited external validation; SF-36
EHRA; European Heart Rhythm Association	EHRA 4 scale; I = no symptoms, II = mild symptoms not affecting daily activity, III = severe symptoms affecting daily activity, and IV = disabling symptoms terminating daily activities.	[45,48]	Simple	Limited validation, applicability

AF, atrial fibrillation; *AFSS*, atrial fibrillation severity scale; *CABANA*, Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation; *CTAF*, Canadian Trial of Atrial Fibrillation; *MANTRA-PAF*, Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation; *NYHA*, New York Heart Association; *QOL*, quality of life; *SARA*, Study of Ablation Versus antiaRrhythmic Drugs in Persistent Atrial Fibrillation.

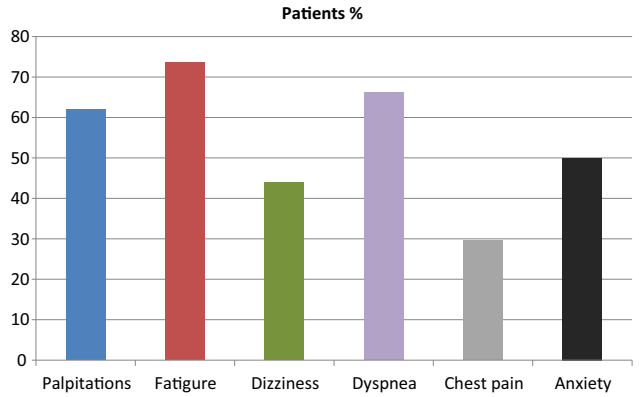

FIGURE 48.1 Distribution of European Heart Rhythm Association score categories of the six symptoms evaluated in the symptom scale. Percentages are given for each category. *Based on data from the "Prevention of Thromboembolic Events—European Registry in Atrial Fibrillation" including 6196 patients with atrial fibrillation and a mean + SD age of 71.8 + 10.4 years with 39.7% women Schnabel RB, Pecen L, Rzayeva N, et al. Symptom burden of atrial fibrillation and its relation to interventions and outcome in Europe. J Am Heart Assoc 2018;7(11):e007559.*

that asymptomatic AF patients are truly asymptomatic without an unconscious adaptation to a life within the range of their physical capacity. It is therefore of great importance to use established questionnaire and to record possible improvements after cardioversions, particularly in the absence of palpitations. It was early recognized that even severely reduced QoL can be normalized reaching the level of the general population after an intervention for rhythm control [29]. Symptomatic and functional improvements have been observed after rate control therapies [30] and several rhythm control treatments including cardioversions [31–33], antiarrhythmic medications, and AF ablation procedures [34–41] albeit not in all studies [42,43] likely depending on the rate of achieved sinus rhythm after a rhythm control intervention. QoL may improve after significant reduction in AF burden even without total elimination of AF [44]. A daily AF burden of more than 2 h was reported as cut-off for a significant impact on QoL [25]. Even though some improvement after AF ablations may be related to a patient's expectancy, the observation that improved QoL after an intervention was directly related to the reduction in AF burden [45] supports a major treatment effect itself. Moreover, cohort studies have reported a maintained improved QoL in patients followed over 10 years after an AF ablation procedure and with a low incidence of progression toward permanent AF [46]. Further studies are mandatory to assess the degree of changes of symptoms and QoL that can be defined as being of clinical importance in the various trials and registries.

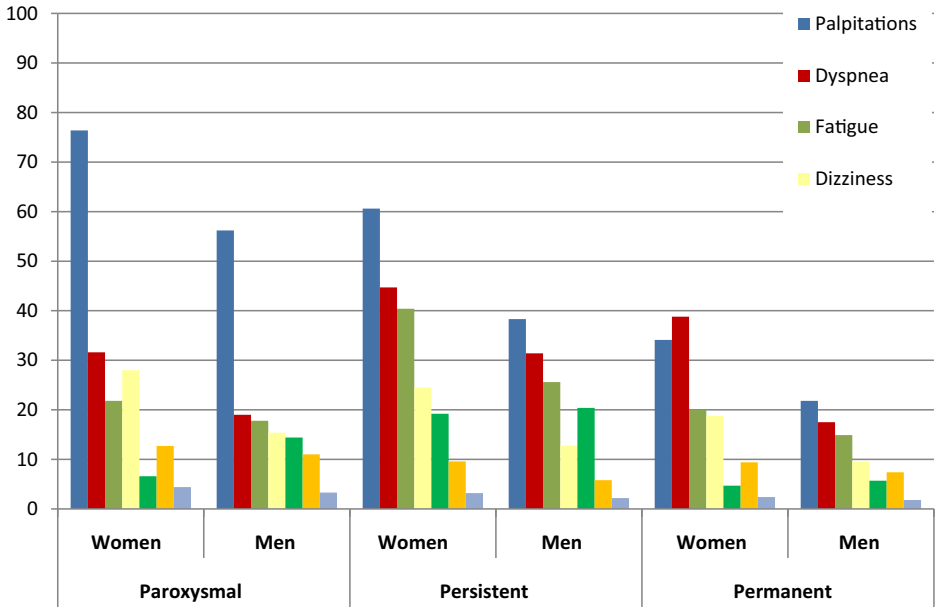

FIGURE 48.2 Distribution of symptoms according to atrial fibrillation type and sex. *Based on data from the Basel Atrial Fibrillation Cohort (BEAT-AF) with 1553 patients with documented AF Blum S, Muff C, Aeschbacher S, et al. Prospective Assessment of Sex-Related Differences in Symptom Status and Health Perception Among Patients With Atrial Fibrillation. J Am Heart Assoc 2017;6(7):e005401.*

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Part XII

Myocardial ischemia and infarction

Chapter 49

Electrocardiographic manifestation of suspected acute coronary syndrome

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Introduction

Coronary heart disease (CHD) is leading cause of morbidity and mortality for men and women in the Western world. Over the last century, CHD has accounted for more deaths than any other causes in the United States and leads causes of death worldwide. Deaths primarily involved ischemic heart disease, acute myocardial infarction, and heart failure [1]. CHD occurs in the presence of inadequate blood supply to the myocardium, which may or may not result from obstructive atherosclerotic narrowing [1].

Acute coronary syndrome (ACS) is the acute manifestation of CHD and is a time-sensitive condition. ACS includes a spectrum of time-sensitive clinical conditions: ST-elevation myocardial infarction (STEMI), non−ST-elevation myocardial infarction, and unstable angina. Prompt and accurate identification of ACS, namely STEMI, are imperative because rapid treatment is associated with improved patient outcomes. Total ischemic time, defined as the time of symptom onset to reperfusion, correlates with infarct size and mortality [2]. Detection and treatment, therefore, aim to minimize total ischemic time. If left undetected, ACS can result in devastating outcomes such as myocardial infarction, heart failure, and death [3].

Current guidelines for patients with suspected ACS recommend the immediate assessment of symptoms, medical history, cardiovascular risk factors, physical examination, electrocardiogram (ECG), and blood biomarkers [4]. Diagnosis of ACS is based predominantly on patient-reported symptoms and the 12-lead ECG, which is the current diagnostic standard and most common diagnostic tool to detect myocardial ischemia and cardiac arrhythmias in clinical practice [1,5].

To date, the 12-lead ECG remains the gold standard used for initial screening, identifying, and evaluating patients with chest pain/anginal equivalents [6]. The ECG is the most widely used initial diagnostic test because it is ubiquitous, noninvasive, and inexpensive and provides vital information about cardiac rhythm, presence of arrhythmias, myocardial ischemia/infarction, and other abnormalities [7−9]. The ECG contains information about cardiac function and underlying conditions that may be latent and is the most effective means of decreasing time to treatment and total ischemic time, which results in improved patient outcomes. ECG is particularly important for detecting silent ischemia, which accounts for 30% of ACS [10].

The American College of Cardiology, American Heart Association, and European Society of Cardiology recommend a 12-lead ECG recorded within 10 min of arrival for all patients who present to the emergency department (ED) with chest pain [11−14]. This recommendation is based on the premise that longer delays are associated with worse outcomes, and ST-segment pattern recognition shortens the delay between first medical contact and life-saving reperfusion therapies [7,11,15].

The accurate and timely diagnosis of ACS, however, remains a challenge. Sex differences in how individuals present with suspicious ACS contribute to the diagnostic challenge. Sex differences manifest differently between men and women in symptom presentation and electrocardiographic changes; both important considerations for triage and identification of ACS. Sex differences between males and females occur due to a complex interplay among cardiovascular structure, function, hormone, autonomic, and genetic factors [16]. Such characteristics are an important trigger for clinical decision-making, such as acquisition of an ECG. Sex differences should be considered in assessing individuals for ACS to prevent missed diagnoses, inadequate treatment, or adverse outcomes. Sex differences in ACS illustrate the importance of sex as a biological variable in this context.

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Sex differences and clinical presentation of ACS

Symptoms

Ischemic symptoms include, but are not limited to, chest pain, upper extremity, mandibular or epigastric discomfort during exertion or at rest, palpitations, dyspnea, and fatigue. Chest pain alone accounts for approximately 6% of ED visits and is one of the most common reasons for hospital admission. Cardiac-related pain is often diffuse, not localized nor positional, nor affected by movement [5]. Patients may have symptoms individually or in various combinations, experience nonchest symptoms (e.g., diaphoresis), present as cardiac arrest, or without symptoms as occurs in silent ischemia [17].

There is ample evidence supporting sex-specific differences in how patients present with suspicious ACS. Females with ACS often present with less typical symptoms, resulting in delayed diagnosis, treatment, and worse outcomes compared to males [18,19]. Females more commonly experience back, jaw and neck pain, nausea and/or vomiting, dyspnea, palpitations, and dizziness, whereas males more frequently present with chest pain [20]. Females tend to report an overall greater number of symptoms compared to males [21]. Older females (>65 years) specifically report encounter of more nausea, fatigue, and dyspnea and overall fewer number of symptoms compared to younger females [19,22]. Less typical symptoms (e.g., fatigue, diaphoresis) may contribute to misdiagnoses or delayed recognition of ischemia in females, which may explain the typically worse clinical outcomes for this group [21,23,24]. In addition to symptom differences, females with ischemic symptoms tend to be older, encounter more arterial hypertension, and have more chronic noncardiac diseases compared to males [21]. Males have higher incidence of STEMI, obstructive coronary disease, rehospitalizations, and percutaneous coronary intervention (PCI). Males are also likely to have a history of smoking, previous MI, or revascularization.

Hess et al. assessed sex differences in clinical presentation, management, and outcome in ED patients with chest pain [20]. They hypothesized sex differences in clinical presentation and pretest probability for ACS was associated with management differences in ED patients with chest pain. Among 970 patients presenting with symptoms suspicious for ACS, nearly 40% were female and had lower prevalence of known coronary artery disease and lower frequency of typical chest pain compared to males [20]. Females had lower rates of acute myocardial ischemia and positive stress test results and were less frequently referred for coronary angiography. Sorenson et al. examined sex differences in clinical presentation in a large contemporary cohort of patients presenting to the ED with signs and symptoms suggestive of ACS [18]. Females were significantly older, had fewer classical risk factors (e.g., smoking, dyslipidemia, history of CHD), and presented with radiating chest pain, dyspnea, nausea, or vomiting; females also reported two or more symptoms more often compared to males [18]. Despite noted sex differences, however, neither diagnostic accuracy nor 2-year outcomes (death or myocardial infarction) differed between females and males. These findings illustrate how sex differences impact clinical decision-making and outcomes in the setting of ACS.

Electrocardiography

The ECG is an integral part of the diagnostic workshop for patients with suspected myocardial infarction. Acute myocardial ischemia is frequently associated with dynamic changes in ECG waveforms [5]. It is, therefore, recommended that several standard ECGs with fixed electrode position be recorded at 15−30 min intervals for the initial 1−2 h or the use of continuous computer-assisted 12-lead ECG records done to detect dynamic ECG changes. Serial ECG acquisition provides critical information and is especially important for identifying myocardial ischemia in individuals with persistent or recurrent symptoms or an initial nondiagnostic ECG [5,25]. Ischemia detection on continuous ECG monitoring is associated with poor outcomes [26]. Clinicians may also consider supplemental leads for patients who present with ischemic chest pain and a nondiagnostic initial ECG. A prior ECG recording is helpful to distinguish new from chronic findings, especially in the prehospital or ED setting where rapid clinical decision-making is often required.

Guidelines recommend an ECG be acquired and interpreted promptly (goal is within 10 min) after first medical contact because morbidity and mortality are directly dependent on the severity and deprivation of blood flow to the myocardium [2,27].

ECG waveforms

Sex differences exist in ECG waveforms and may be present in both normal and ischemic conditions. In the first decade of life, ECG parameters in males and females are similar regarding resting heart rate, PR interval, QRS duration and voltage, T-wave amplitude, T axis, ST-segment location, QRS-T angle, AT interval, and the frequency of normal U waves. Likely related to hormones, in adolescence, females have a higher resting heart rate and longer QT and QT_c intervals [28]. In adulthood, sex differences in QRS voltage are maximum <40 years and duration is longer in males than females [1]. ST amplitudes are higher in young males compared to young females; yet differences in the ECG tend to diminish with advancing age.

ECG signs of ischemia

Changes in intracellular action potential in myocardial ischemia, injury, and infarction frequently result in changes in ECG waveforms [29]. Electrocardiographic manifestations suggestive of ACS (in absence of left ventricular hypertrophy and bundle branch block) include ST elevation, ST depression, and/or T-wave inversion (Fig. 49.1). ECG changes occur before myocardial infarction, providing the ability to intervene to restore blood flow before myocardial cell death ensues. Earlier manifestations of myocardial ischemia include typical T-wave and ST-segment changes. A current of injury flows from the uninjured portion toward the injured portion, resulting in ST-segment deviation indicative of ischemia. ST-segment depression reflects the typical manifestation of "demand-related" ischemia; these changes reflect injury to the subendocardium, which is the innermost layer of the heart. The current flows away from the surface electrode, which results in ST-segment depression. ST-segment elevation reflects subepicardial or transmural ischemia injury and reflects supply-related ischemia, which is caused by sudden thrombotic occlusion of one of the major vessels in the heart. Supply-related ischemia affects the entire thickness of the myocardium, making immediate intervention imperative to salvage myocardium. ECG manifestations of ischemia, such as ST elevation caused by supply-related ischemia, can localize the area of ischemia myocardium and identify the culprit artery [30]. The ST segment is more labile in females compared to males, and females encounter a greater degree of nonspecific ST-segment deviation [16].

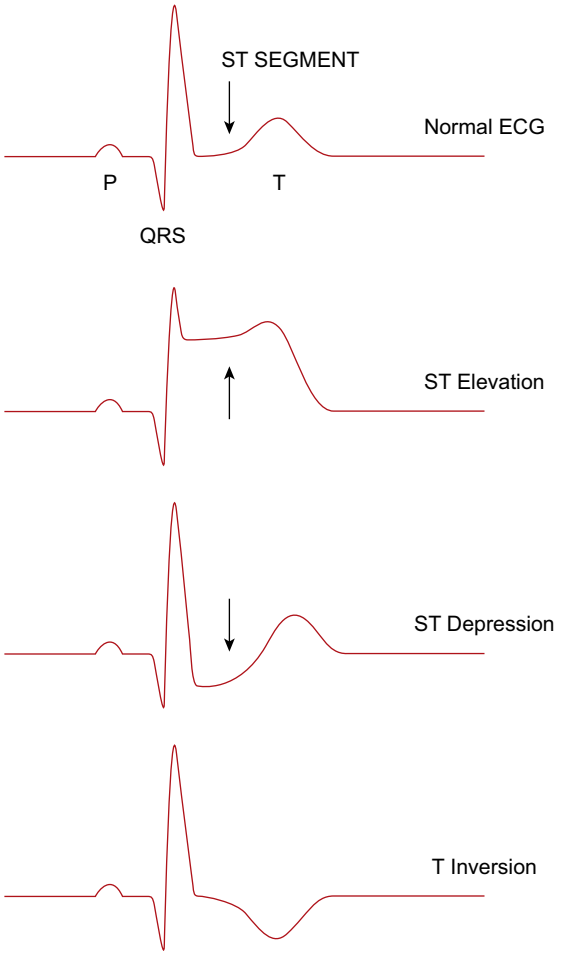

FIGURE 49.1 ECG changes in the ST-T segment indicative of acute myocardial ischemia and/or infarction.

Other ECG signs associated with acute myocardial ischemia include arrhythmias, intraventricular bundle branch blocks, atrioventricular conduction delays, and loss of precordial R wave amplitude, which is a less specific finding [5].

The presence of acute ischemic ST-T segment changes on the initial ECG, often conducted at presentation to the ED, is associated with a higher risk of cardiac events [31]. Acute ischemic changes are unpredictable and dynamic in nature, which suggests that a single snapshot 12-lead ECG is inadequate and continuous or serial ECG monitoring is diagnostically superior [32]. In a study of individuals presenting with chest pain symptoms to the ED, the sensitivity of prehospital ECGs significantly increased when considered in conjunction with the initial hospital ECG [32]. Fig. 49.2 illustrates how serial ECG recordings enhance the diagnostic sensitivity for ACS, as compared to a single tracing.

ECG findings direct clinical decision-making, including activation of the cardiac catheterization laboratory for patients suffering from STEMI. The presence of ischemic signs may drive the decision for ED clinicians to activate the catheterization laboratory for patients suffering from acute myocardial infarction; this extends into the prehospital period where paramedics may analyze ECGs acquired in the ambulance and activate the cardiac catheterization laboratory prior to hospital arrival [33]. Accurate interpretation of ECG findings, moreover, is crucial in establishing diagnoses.

ECG criteria for myocardial ischemia and infarction

Traditionally, the standard criteria for ischemia diagnosis were 0.2 mV or more (in leads V_1, V_2, or V_3) or 0.1 mV or more (in all other leads) of ST elevation at the J point in two or more contiguous leads; ST depression of 0.1 mV in two or more contiguous leads; and inverted T waves of 0.1 mV in leads with predominant R waves [34]. The J point is the junction between QRS determination and ST-segment onset and determines the magnitude of ST-segment shift [25]. J-point elevation decreases with increasing age in males, but this has not been observed in females who have less J-point elevation compared to males

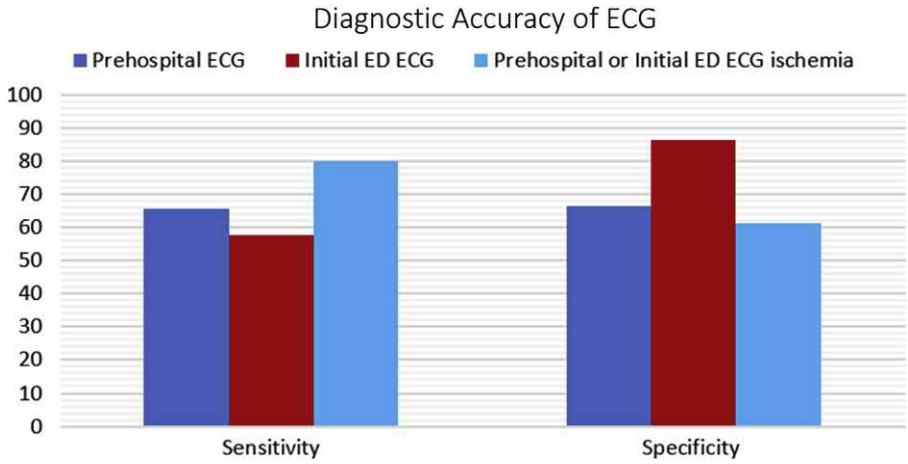

FIGURE 49.2 The sensitivity and specificity of a prehospital ECG alone, the initial ED ECG alone, and in conjunction. There was a significant increase in sensitivity with a reduction in specificity when either the prehospital ECG or the initial ED ECG had evidence of myocardial ischemia.

at baseline [17]. Contiguous leads are grouped as anterior leads (V_1—V_6), inferior leads (II, III, aVF), or lateral/apical leads (I, aVL).

Recent efforts have been made to increase the sensitivity and specificity of the standard 12-lead ECG. New ECG criteria for myocardial ischemia were first published in 2007 that factored in sex differences between males and females [35]. As indicated in Table 49.1, [25] published updated guidelines that factored in sex differences between men and women in ECG criteria. Criteria updates emphasize the importance of sex differences in diagnosing acute myocardial ischemia and/or infarction [25]. These criteria also include age differences [17,25]. It is imperative that clinicians be familiar with sex differences in ECG criteria in order to optimize diagnostic accuracy.

Flesichmann et al. compared differences in sensitivity and specificity based on prior and current ECG criteria for ischemia and assessed whether revised ECG criteria improved ED identification of patients with ACS [36]. Patients presenting to the ED with chest pain or anginal equivalent were included in the study. A total of 120 patients had nondiagnostic initial ECGs on arrival. After updated criteria were applied, 12(10%) had initial ECGs diagnostic of ischemia (Fig. 49.3). The goal of these revised criteria was to improve the sensitivity of the initial ECG for acute myocardial ischemia and/or infarction, especially in females. Findings revealed sensitivity for ACS was increased, and those with ECG diagnostic of ischemia by revised (but not prior) standard criteria also had a trend toward increased 1-year mortality, which highlights the importance in accurately identifying males and females with ACS [36].

ST-T segment elevation

Prolonged new convex ST-segment elevation reflects acute coronary occlusion, particularly when associated with reciprocal ST-segment depression [5]. Reciprocal changes are important for distinguishing STEMI from confounding factors including pericarditis or early repolarization changes. The magnitude of ST-segment shift is determined by the J point (the junction between QRS determination and ST-segment onset). J-point determination is recommended at the QRS onset [5]. Sex differences require different cut-off points for women because J-point elevation in healthy women in anterior leads (V_2 and V_3) is less than in men. ST amplitudes are sex dependent, but providers do not

TABLE 49.1 ECG manifestations of acute ischemia (in absence of left ventricular hypertrophy and left bundle branch block).

ST elevation: New ST elevation at the J point in two contiguous leads with the cut-point: > 1 mm in all leads other than leads V_2—V_3, where the following cut-points apply: > 2 mm in men >40 years; > 2.5 mm in men <40 years, or >1.5 mm in women regardless of age.
ST depression and T-wave changes: New horizontal or downsloping ST depression > 0.5 mm in two contiguous leads and/or T inversion >1 mm in two contiguous leads with prominent R wave or R/S ratio >1.

From "Universal Definition of Myocardial Infarction," by Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Circulation 2018;138(20):e618—51.

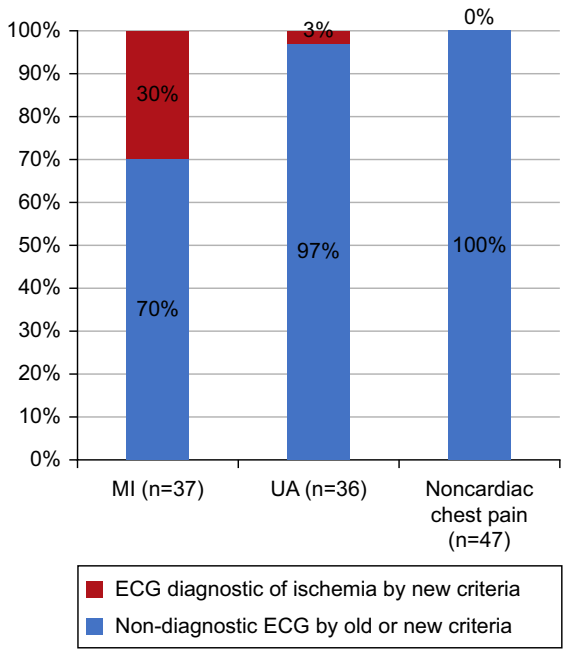

FIGURE 49.3 Relation of final diagnosis to new universal criteria for myocardial ischemia/infarction in 120 individuals presenting to the ED with initial nondiagnostic ECG. *MI*, myocardial ischemia; *UA*, unstable angina. *Adapted from Fleischmann KE, Zegre-Hemsey J, Drew BJ. The new universal definition of myocardial infarction criteria improve electrocardiographic diagnosis of acute coronary syndrome. J Electrocardiol. 2010;44(1):69–73.*

routinely consider differences in clinical practice. Amplitude differences occur because females have smaller epicardial coronary arteries compared to males, even after accounting for body and LV mass. ST amplitudes are higher in young males compared to young females, yet this tends to diminish with age [1]. Increased R-wave amplitude and width commonly accompany leads with ST elevation.

Case study

Fig. 49.4 represents the prehospital ECG of a 64-year-old white female who presented with vague complaints of not feeling well. She had a known history of hypercholestremia, hypertension, diabetes, and a prior MI. Upon arrival to the ED, she went directly to the cardiac catheterization laboratory for PCI and received a stent to her RCA. She had a final hospital diagnosis of STEMI.

Males more commonly have ST-segment elevation on their initial hospital ECG compared to females [18]. Sorensen et al. examined the differences between males and females presenting to the ED with highly suspicious ACS and found males had significantly more ST-segment elevation (25.9% versus 14.3%, $P < .001$) and left or right bundle branch block (10.5% versus 7.5%, $P=.013$) compared to females [18]. Compared to males, females with ST elevation on the initial ECG are over three times as likely to be diagnosed with ACS.

Patients who develop new ST-segment elevation in two contiguous leads or new bundle branch blocks with ischemic repolarization patterns are designated as STEMI for immediate treatment strategies. PCI is the treatment of choice in STEMI; electrocardiographic findings, therefore, are critical for identifying STEMI and facilitating triage of STEMI patients to PCI. Fig. 49.5 illustrates ST elevation in a male presenting with ACS symptoms.

ST depression and T-wave changes

Electrocardiographic changes in the ST segment and T waves are recognized as potent indicators of ischemia and potential infarction. Recommendations for standardization and interpretation in the ECG include age and sex-specific criteria for ST elevation and lead-specific criteria for ST-depression [37]. New horizontal or downsloping ST-depression $\geq$ 0.5 mm in 2 contiguous leads and/or T inversion $>$ 1 mm in 2 contiguous leads with prominent R wave or R/S ratio $>$1. The greater number and more profound ST-segment shifts or T-wave inversions involving multiple leads/territories are associated with a greater degree of myocardial ischemia and worse prognosis [5]. For example, ST-segment depression $>$1 mm in six leads may be associated with multivessel disease or left main disease [5]. ST-segment depression and/or T-wave inversion are significantly associated with increased odds of an ACS diagnosis in men and women (Figs. 49.6 and 49.7).

In a study examining post-MI individuals, women encountered significantly more lateral ST depression ($V_{5–6}$, I, aVL) and T-wave inversion in anterior and lateral regions compared to males [38]. There were no sex differences in inferior T-wave location compared to men. Standard ECG was obtained 5–7 days after first MI and evaluated for associations with sex and cardiac events (cardiac death, nonfatal MI, or unstable angina). ECGs were analyzed by a core laboratory and the ECG classification criteria for postinfarction trials were applied [39]. ST depression was defined as ST-segment depression $>$ 1 mm, at J+80 ms.

T wave

Diagnostic criteria consider sex differences in T-wave amplitude, which is important in the setting of acute myocardial ischemia/infarction. The upper limit of normal for males is 1.4 mV and for females is 1.0 mV. Normal variation in T-wave morphology between sex differences may occur in the right precordial leads. T-wave inversion in V_2 is frequently regarded as normal in females more often than males [1]. During acute episodes of chest pain, pseudonormalization of previously inverted T waves may indicate myocardial ischemia [17].

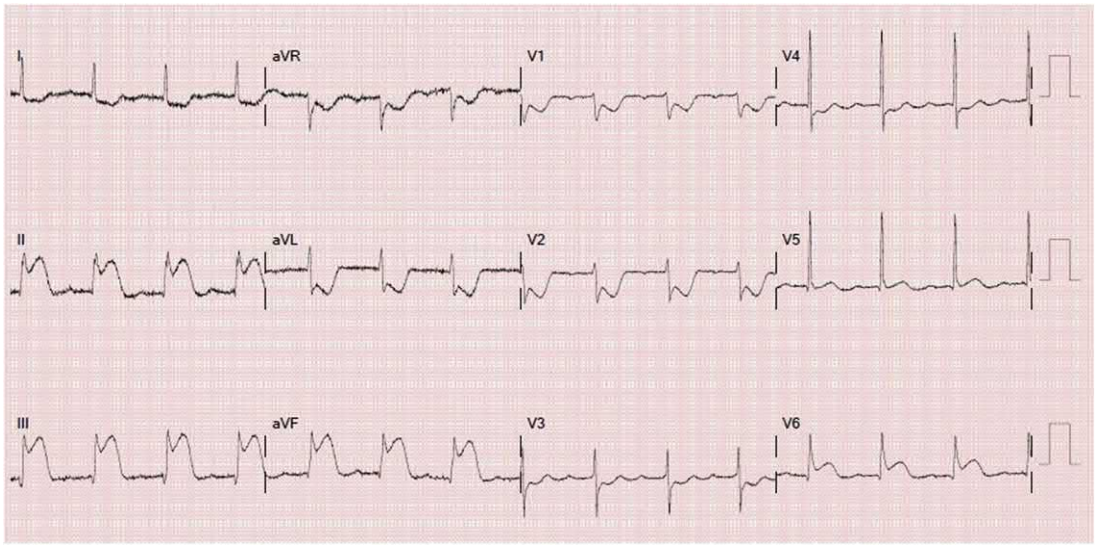

FIGURE 49.4 ST elevation in II, III, and aVF with reciprocal changes in I, aVL, and aVF.

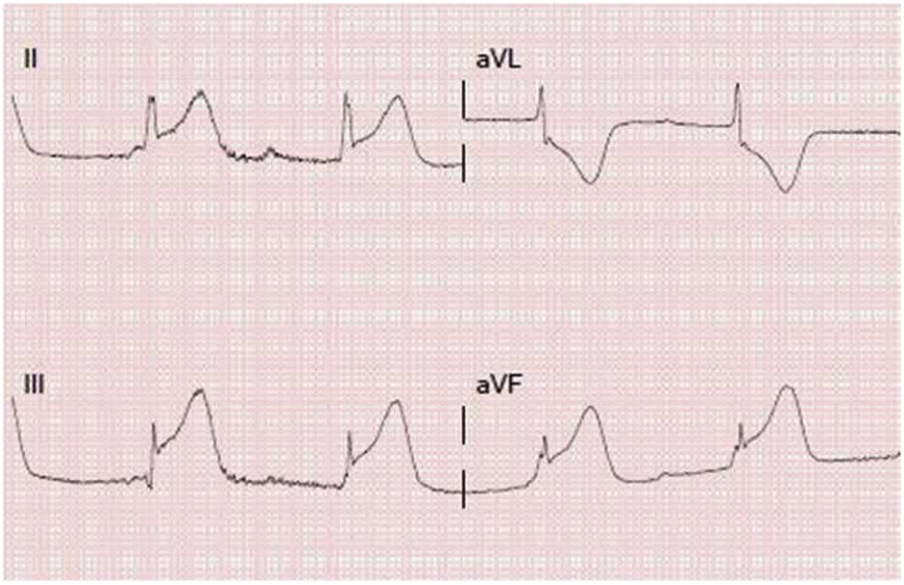

FIGURE 49.5 ST elevation in II, III, and aVF in 51-year-old male with ACS symptoms.

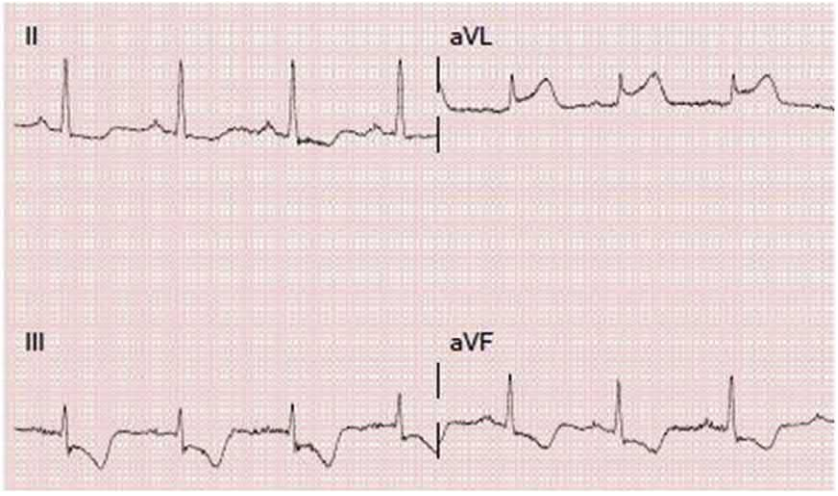

FIGURE 49.6 ST depression in II, III, and aVF in 54-year-old female with ACS symptoms.

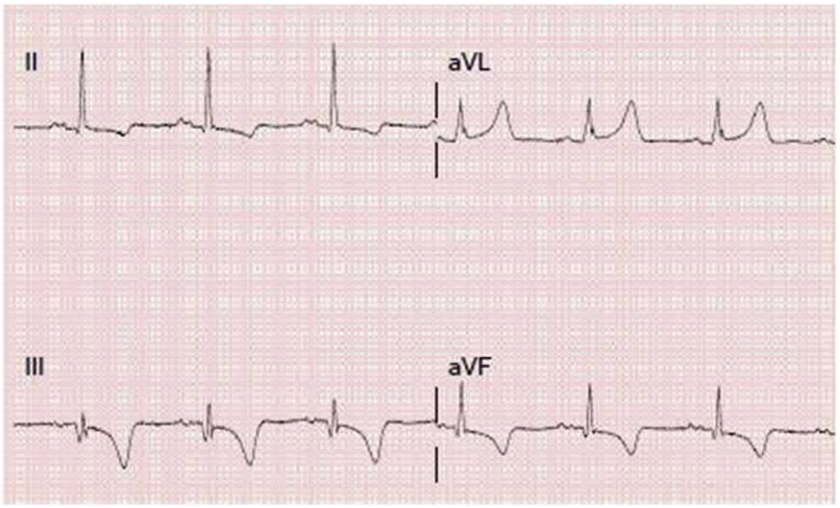

FIGURE 49.7 T-wave inversion in II, III, and aVF in 52-year-old female transported by ambulance for chest pain.

Wellens type 1 versus type 2 ECG patterns

Wellens syndrome signifies an imminent occlusion of the left anterior descending artery. Electrocardiographic changes include deep symmetrical anterior T-wave inversion (type 1) or subtle positive-negative biphasic anterior T waves (type 2). To date, sex differences have not yet been observed in Wellens types 1 and 2.

Q wave

Q waves increase the prognostic risk, and new Q waves indicate myocardial necrosis, which begins minutes/hours after the myocardial insult. There are limited data regarding sex differences among patients after MI. In a study that examined ECG parameters in 838 patient 5−7 days after their first MI, heart rate was faster and QT_c duration was longer in females compared to males [38]. In contrast, QRS duration was shorter in females compared to males. This reflects underlying anatomical differences between females and males; on average, females have a smaller left ventricular mass and shorter QRS duration compared to males [16].

Conclusion

Myocardial ischemia and/or infarction is defined from individuals' clinical presentation and ECG results. Sex differences exist between males and females and are important to distinguish in order to optimize the accurate and rapid diagnosis of ACS. Sex-based electrocardiographic criteria have been established to increase the sensitivity and specificity of the ECG. ECG interpretation, therefore, should be optimized using these criteria.

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Chapter 50

Acute myocardial infarction and cardiogenic shock arrhythmias

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Acute myocardial infarction is defined as myocardial necrosis, which develops from sustained ischemia lasting longer than 30 min. During approximately 2 weeks, the necrosis heals by fibrotic scar from the periphery toward the center of ischemia. This scar matures and remodels within 2 months following the myocardial infarction [1]. Ventricular arrhythmias complicate all phases of myocardial infarction and they can result in a life-threatening condition.

Obstructive atherosclerotic disease of the epicardial coronary arteries is the most common cause of acute myocardial infarction. Recent findings show sex differences in the pathophysiology of coronary events. Men usually present with more significant obstructive disease of coronary arteries than women, whereas microvascular coronary dysfunction and distal microvascular embolisations probably play a more important role in the etiology of acute ischemia in women. Moreover, women tend to suffer from myocardial ischemia originating from atypical pathophysiological mechanisms of coronary artery disease such as spontaneous coronary artery dissection or coronary artery spasm (Fig. 50.1). Concerning atheromatous plaque formation, characteristics differ according the age and sex. Typical finding in younger (premenopausal) women is a plaque erosion. It is often seen in calcified plaques, which are lipid poor with few inflammatory cells. Endothelial cell apoptosis plays a role in the thrombus formation. On the other hand, a plaque rupture with a large necrotic core and disrupted fibrous cap infiltrated by macrophages and lymphocytes is observed more commonly in men and older women [2–5] (Fig. 50.2).

Women develop their first myocardial infarction in older age than men. The average age is 72 years compared to 65 years in men. Older age in women also brings along more comorbidities, such as diabetes mellitus, hypertension, or lipid metabolism disorders. Men, though younger, smoke cigarettes more often. Female sex hormones are thought to play a protective role in premenopausal women and contribute to the delayed disease onset. The complex mechanism of estrogen influence is not understood completely, but direct effect of estrogen on the vascular system includes increased release of nitric oxide leading to vasodilation, regulation of prostaglandin production, antiinflammatory effects, and inhibition of smooth muscle proliferation. Estrogen lowers the accumulation of cholesterol in the arterial wall and also the platelet aggregation. Estrogen has calcium antagonistic properties, which are endothelium independent. Estrogen also modulates the neurohormonal system and influences abnormal release of catecholamines. Estrogen depletion after menopause increases endothelial dysfunction and lipid depositions, insulin resistance, lipid metabolism disorders, hypercoagulation, and inflammation. These effects summed up accelerate atherosclerotic vessel changes [6,7] (Fig. 50.3). In the light of these facts, it is interesting that results from clinical trials of exogenous estrogen supplementation therapy in postmenopausal women bring controversial results.

On the cellular level, acute myocardial infarction is associated with many electrophysiological changes, which may cause different bradyarrhythmias and tachyarrhythmias. Hypoxia leads to intracellular acidosis, which is the pathological substrate for acceleration of hydrogen, sodium, and calcium ions exchanges through the cellular membrane. Eventually, it is the calcium overload and swelling of the cell itself that is responsible for the damage of myocytes. Resting membrane potential rate increases and the myocyte action potential is prolonged [8].

Macroscopically, the ischemia and later the scare formation are the underlying causes for reentry circuit, based on dispersion of refractoriness among the cells of the central and surrounding part of the ischemic zone. These changes lead to conduction, refractoriness, and automaticity abnormalities and contribute to the onset of arrhythmias.

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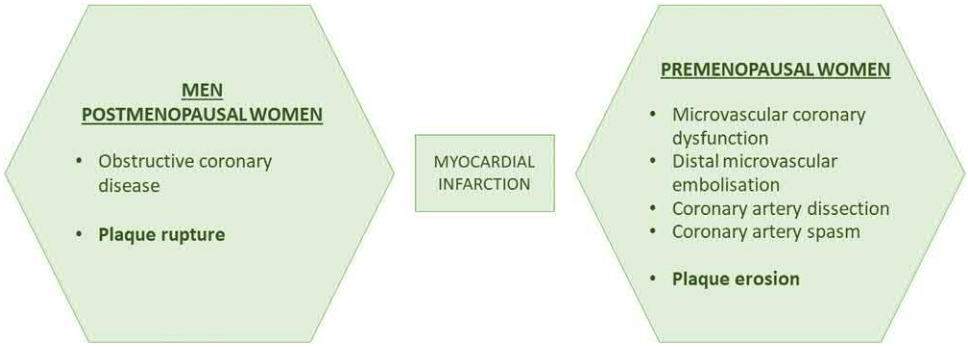

FIGURE 50.1 Differences in pathophysiology of coronary events. Pathophysiology of coronary events differs by sex. In men and postmenopausal women, the majority of events are caused by obstructive coronary disease and plaque rupture. On the other hand, premenopausal women present more often with atypical pathophysiological mechanisms as distal microvascular embolization, coronary artery dissection, or spasm and plaque erosion.

CAUSES OF ARTERIAL THROMBOSIS		
	PLAQUE RUPTURE	PLAQUE EROSION
PLAQUE CORE	Lipid rich	Lipid poor
FIBROUS CAP	Thin	Compact
INFLAMMATORY CELLS	Abundant - macrophages	Few - neutrophils
BLOOD LIPIDS	High LDL	High tryglycerides
PREDOMINANCE	Male, postmenopausal female	Premenopausal female

FIGURE 50.2 Causes of arterial thrombosis. Differences in plaque properties in case of rupture or erosion.

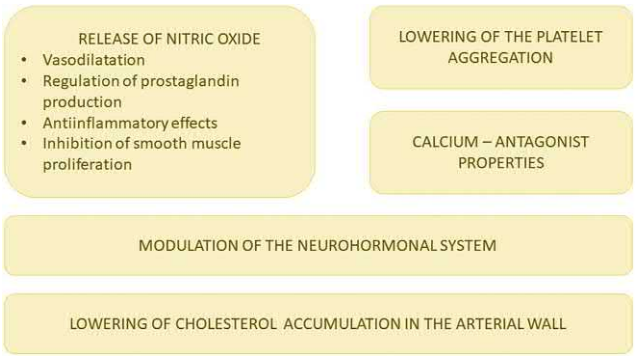

FIGURE 50.3 Oestrogen influence on coronary artery disease onset delay in premenopausal women.

Reentry circuit may have an anatomical or a functional substrate. It is either formed around a scar originating from former ischemia or it can be based on functional inequality in conduction or a block of conduction in some parts of the myocardium. Approximately 20% of acute myocardial infarctions associate with a left ventricular dysfunction, which is often only transient, and the ventricular function normalizes within a few weeks after the myocardial infarction. Mechanical stretching of a failing ventricle in combination with a high sympathetic activity during acute ischemia can result in a focal trigger of ventricular arrhythmias. Ventricular tachycardia (VT) occurrence during the first 10 minutes after a coronary occlusion is due to a reentry within the ischemic myocardium. Quite large circuits with diameters as large as l–2 cm originate from a moderate reduction in conduction velocity and delayed recovery of excitability. An area of a functional conduction block provides the central obstacle for a reentrant circuit. However, excitability within these regions may recover and the cells in conducting pathways may temporarily become inexcitable. During reperfusion, the extra- and intracellular ion concentrations normalize and the cellular action potential duration recovers. These changes are not homogenous, however, due to the fact that the blood flow restoration is uneven. This results in dispersion of refractoriness, which leads to a reentry circuit. Electrically inactive scar tissue forms the reentrant circuit at about 2 months after the acute myocardial infarction. That is the most common cause of sustained monomorphic VT in chronic phase of ischemic heart disease [1,8].

The last two decades brought new treatment methods, including acute revascularisation and medical therapy (antiplatelet drugs, beta-blockers [BBs], angiotensin-converting enzyme inhibitors [ACEIs], and statins), which substantially improved therapeutic outcomes in acute myocardial infarction patients. However, approximately 10% of myocardial infarction survivors still face a high risk of sudden death within the first year following the acute

episode. Sudden death due to sustained VT or ventricular fibrillation (VF) accounts for about a half of all deaths in these high-risk patients [1].

As a major community study focused on ventricular arrhythmias after myocardial infarction spanning 20 years shows the median delay of onset after ischemia for ventricular arrhythmias is 1.4 h and the majority (approximately 80%) occur in first 48 h. Ventricular arrhythmias are more common in patients with STEMI, atrial fibrillation, higher Killip class III or IV, lower ejection fraction of left ventricle, and in women. They are also more common in patients without preexisting cardiac disease [9]. There is not clear relationship between early onset VF/VT (occurring within 48 h of the ischemia) and mortality. Analyzing sustained ventricular arrhythmias, some studies show that those detected during the early post-MI period may be associated with increased 30-day mortality. No protracted risk over the long term was found, though [10–12]. Nonsustained VT in the early phase post-MI does not contribute to mortality risk [13]. If sustained VF or VT occurs later than 48 h after the myocardial infarction onset, the all-cause mortality is significantly higher. Meanwhile, the HORIZONS-AMI trial results proved that the sustained VT/VF after primary PCI is not significantly associated with 3-year mortality [14].

Sources contradict on the risk rate of ventricular arrhythmia in acute myocardial infarction in women. While some studies state that women and men appear to be at similar risk for the development of ventricular arrhythmias after myocardial infarction, others hint otherwise [15]. Not only myocardial infarction incidence but also myocardial infarction–related death rate declined over the past decades, thanks to the improvement of diagnostic and therapeutic methods. Surprisingly, men benefited from this development more then women. Especially younger women in age group of under 55 years remain in an increased risk of death. Having said that, the 1-year and also the 5-year survival rate is lower in women than in men. Nevertheless, it is probably the social, environmental, and community factors, rather than gender and sex differences, that are responsible for the worse outcomes in women.

It usually takes women more time to seek help while experiencing symptoms of acute myocardial infarction. This is often due to a lack of awareness of danger or due to atypical symptoms [16].

Moreover, the group of women is not homogenous regarding race. The black women have a higher prevalence of myocardial infarction and also higher incidence of sudden cardiac death as the first manifestation of myocardial infarction than white women. Their survival rate after cardiac arrest before admission is about one-third that of white women [17]. Asian Indian women develop more cardiovascular risk factors and comorbidities as hypertension, diabetes mellitus, and lipid metabolism disorders at a younger age than white women. Thus, the Asian Indian women group show greater mortality compared with white women. Concerning black or Hispanic women, not only racial but also social factors play a role in all this. Some studies point out that the delayed access to treatment of myocardial infarction may be due to lower education and socioeconomic barriers. According to guideline-based recommendations, women are undertreated. Invasive treatment as reperfusion is underused and medical therapy is underprescribed. This leads to increased rates of readmission, reinfarction, and deaths in the first year after MI. In addition, the situation is worsened by suboptimal adherence to evidence-based recommendations in women [6].

Early administered medical therapy including BBs and ACEIs or angiotensin receptors blockers (ARB), antiplatelet drugs, and statins reduces the risk of ventricular arrhythmias in acute myocardial infarction. A course of BBs is associated with a 21% reduction in mortality, a 30% reduction in sudden death, and a 25% lower reinfarction rate with similar benefits in women and men [18,19]. Nonselective BBs should be avoided in patients whose acute myocardial infarction is due to coronary arterial vasospasm because this medication can exacerbate vasospasm [20]. Having said that, there is a proof of higher incidence of vasospasmic etiology of acute myocardial infarction in women. Thus, women could benefit from selective BB treatment. The reality is that women are in general undertreated by BBs in comparison to men. Furthermore, guidelines do not recommend any sex-based practice (Figs. 50.4 and 50.5).

Early VF/VT in acute phase of myocardial infarction occurred in 4.4% of the GUSTO V trial population. 30-day mortality differed in correlation with arrhythmias (22% in patients with early VF/VT compared to 5% in patients without this condition). Patients receiving ACEI/ARB in the acute phase of myocardial infarction showed lower 30-day mortality compared to patients not receiving this therapy [10]. When comparing prescription of the ACEI/ARB regime to women and men, women are undertreated. This fact could increase the risk of ventricular arrhythmias onset in acute myocardial infarction in women.

Prompt administration of reperfusion therapy in acute myocardial infarction also reduces the risk of ventricular arrhythmias. Cardiac catheterization and timely reperfusion is less frequently available for women due to their less frequent and later referral to the procedure (Fig. 50.6). These facts correspond with sex differences in duration of prehospital delay. Men arrive at the hospital in the second hour and also in the sixth hour after myocardial infarction symptoms onset more often than women [21] (Fig. 50.7).

Women are less likely selected to receive an ICD for primary or secondary prevention of sudden cardiac death compared with men [22]. The reason to this is complex. Women present with left ventricular systolic dysfunction

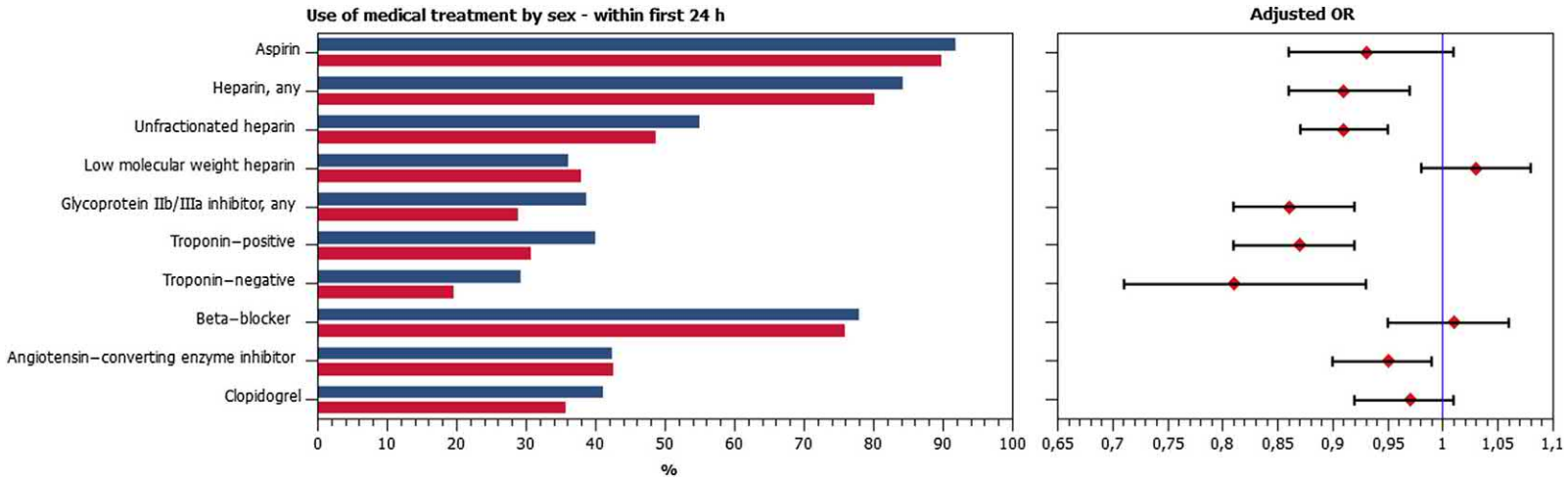

FIGURE 50.4 Sex differences in medical treatment in acute myocardial infarction within first 24 h. Comparison of acute medical treatment of myocardial infarction in men versus women. Adjusted odds ratio shows likeliness of a particular treatment in women. *Modified from Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB et al. Gender disparities in the diagnosis and treatment of Non-ST-segment elevation acute coronary syndromes. Large-scale observations from the CRUSADE. J Am Coll Cardiol 2005;45(6):832−837.*

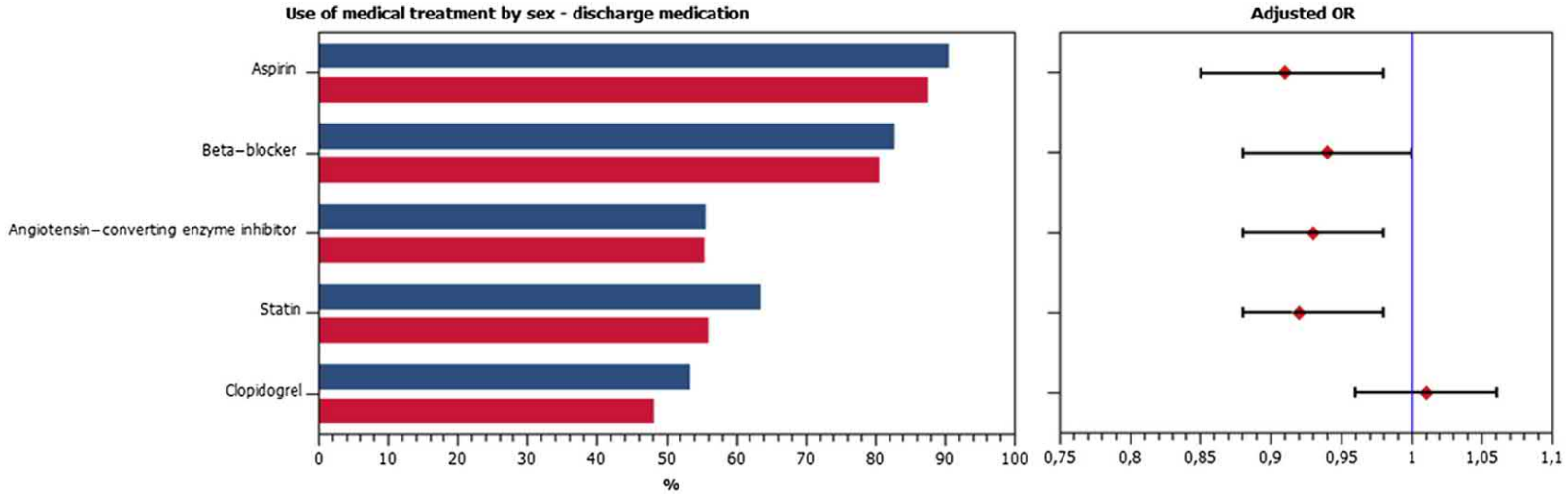

FIGURE 50.5 **Sex differences in discharge medication in acute myocardial infarction.** Comparison of myocardial infarction discharge medication in men versus women. Adjusted odds ratio shows that women are undertreated in comparison to men. *Modified from Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB et al. Gender disparities in the diagnosis and treatment of Non-ST-segment elevation acute coronary syndromes. Large-scale observations from the CRUSADE. JACC (J Am Coll Cardiol) 2005;45(6):832–837.*

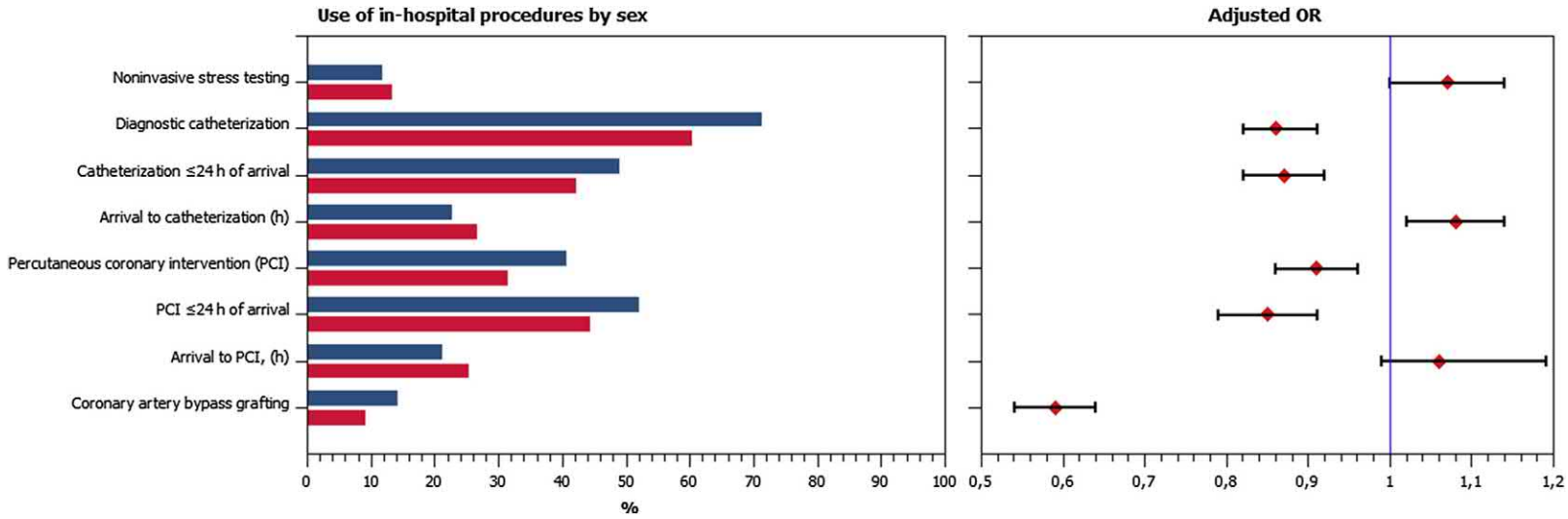

FIGURE 50.6 Sex difference in diagnostic and therapeutic procedure use in acute myocardial infarction. In acute myocardial infarction, women recieve more often noninvasive than invasive diagnostic procedures and revascularisation is underused in women. *Modified from Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB et al. Gender disparities in the diagnosis and treatment of Non-ST-segment elevation acute coronary syndromes. Large-scale observations from the CRUSADE. J Am Coll Cardiol 2005;45(6):832−837.*

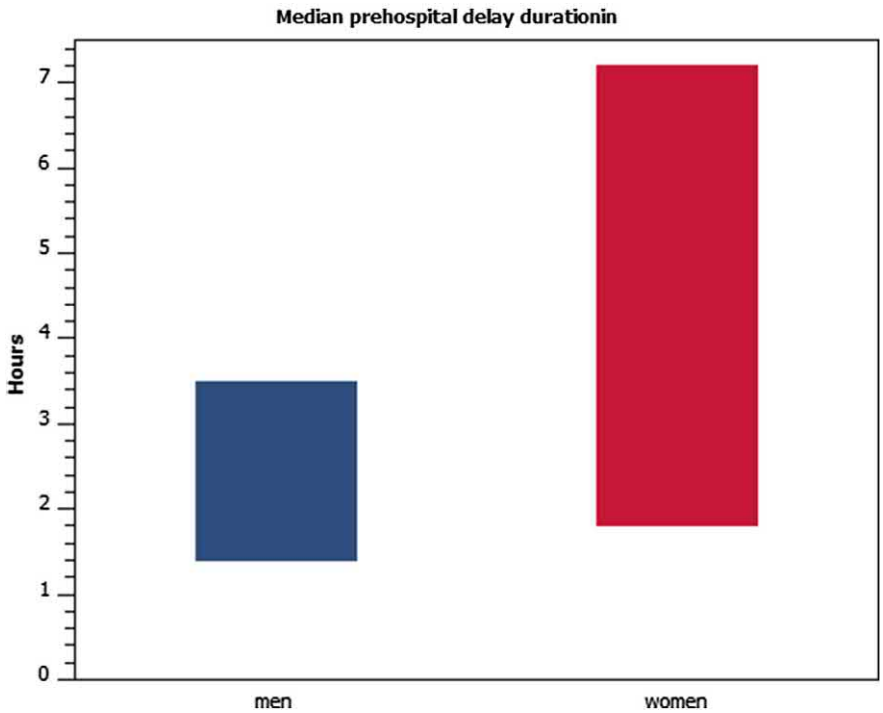

FIGURE 50.7 Sex difference in admission delay in acute myocardial infarction. Women have longer delay between symptoms onset and admission to hospital.

less often. They develop an isolated diastolic dysfunction more frequently. Last but not least, women are often underrepresented in clinical trials and therefore sex and gender-specific results are scarcely available.

Acute myocardial infarction may also be complicated by atrioventricular conduction disturbances, sinus node dysfunction, and supraventricular tachyarrhythmias. Overall, 7% of patients with acute myocardial infarction develop significant bradyarrhythmias. These include atrioventricular node dysfunction. 12%–13% of patients presenting with an inferior myocardial infarction develop an atrioventricular blockade. It is associated with increased 30-day and 1-year mortality. Women are at greater risk of developing a high-degree atrioventricular block in the setting of myocardial infarction. Seriousness of this problem depends on the type of myocardial infarction. STEMI is more often associated with a high degree of atrioventricular blockade, but there is a higher possibility of spontaneous resolution without the need of permanent pacemaker implantation (compared to NONSTEMI). Bradyarrhythmias accompanying inferior myocardial infarction are usually transient and are associated with atrioventricular node ischemia. High-degree atrioventricular block associated with anterior myocardial infarction is a sign of large area of ischemia and therefore has a worse prognosis [23,24].

Atrial fibrillation is the most common supraventricular arrhythmia in acute myocardial patients. Patients with atrial fibrillation also have a higher incidence of VF after MI. New onset of atrial fibrillation occurs in 6%–9% of patients with acute myocardial infarction. It increases the 90-day mortality rate due to a more frequent association with heart failure and stroke in these patients. Women and older patients are at greater risk of developing atrial fibrillation in acute phase of myocardial infarction [25].

Cardiogenic shock occurring in acute phase of myocardial infarction is related to the size of ischemic area and poses a higher risk of ventricular arrhythmias. Alternative causes of the shock include mechanical complications of acute myocardial infarction, as a rupture of free ventricular wall or interventricular septum or right ventricular infarction. It usually develops within first 24 h after the myocardial infarction onset and the incidence oscillates between 5% and 8% in STEMI and 2.5% in NONSTEMI. Mortality remains very high, approximately 50%–70%. Early revascularization may cut the mortality rate. Women often present with smaller infarct size and less extensive coronary artery disease. On the other hand, they are older, have more comorbidities, and are at increased risk of cardiogenic shock development. Early revascularization is the golden standard in the cardiogenic shock treatment. In refractory cases, intraaortic balloon pump or one of left ventricular assist devices are optional [26].

Cardiogenic shock can be complicated by supraventricular and ventricular arrhythmias. Arrhythmias can significantly worsen hemodynamic conditions and contribute to the creation of the vicious circle. There is not

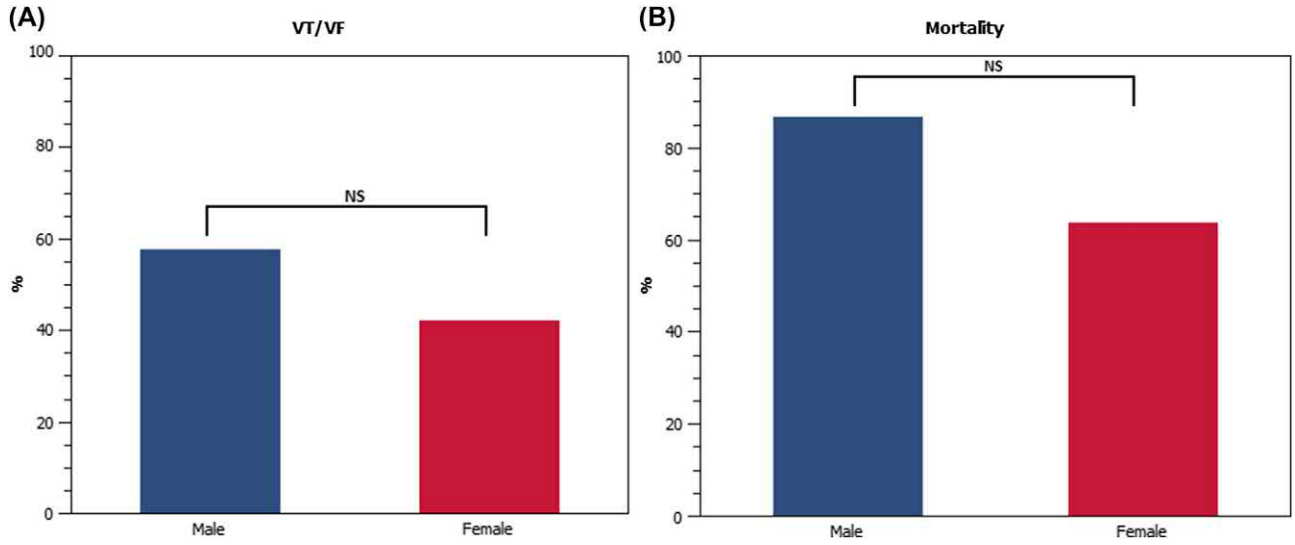

FIGURE 50.8 Sex difference in life-threatening arrhythmias during cardiogenic shock. No sex difference was found in the incidence of ventricular tachycardia (VT) or ventricular fibrillation (VF) – part A, neither in mortality in patients with VT/VF occurrence during cardiogenic shock – part B. *Modified from Goldberg RJ, Gore JM, Alpert JS. Cardiogenic shock after acute myocardial infarction. NEJM 1991;325(16):1117–22.*

a "typical" arrhythmia associated with cardiogenic shock. In general, there is a lack of information on arrhythmias linked to cardiogenic shock. One of the few studies considering this topic included 797 patients with acute myocardial infarction. 78 of them (9.7%) developed cardiogenic shock, of which 52 were men and 26 women, in the age of 66 ± 10 years. 30 men suffered at least one episode of VF/VT, and 26 of them died. 11 women experienced malignant arrhythmia, and 7 of them died. VF/VT had no influence on mortality on the probability level of $P = 0.591$. No sex-related difference was detected in either frequency of cardiogenic shock occurrence ($P = 0.235$) or mortality rate ($P = 0.178$) [27] (Fig. 50.8). Medical therapy of arrhythmias in the context of cardiogenic shock is problematic. The low ejection fraction, heart failure, and unfavorable hemodynamic status exclude the use of some antiarrhythmic drugs. Thus invasive treatment including ablation may be the most rational option to improve the hemodynamic situation [28].

In conclusion

Men and women differ in the etiology of acute myocardial infarction. Men usually present with more significant obstructive disease of coronary arteries. Microvascular coronary dysfunction, distal microvascular embolisations, and atypical pathophysiological mechanisms of coronary artery disease as coronary artery dissection or spasmus are more common in women. Characteristics of the atheromatous plaque formation differ according the age and sex. In younger women, typical plaque erosion is observed, and in men and older women, more common plaque rupture is observed. At the time of myocardial infarction, women are older and present with more comorbidities. Myocardial infarction incidence and also infarction-related deaths rate declined over the past decades, thanks to the improvement of diagnostic and therapeutic methods. Surprisingly, men benefit from this development more than women. Especially younger women in age group of under 55 years remain in an increased risk of death. The social, environmental, and community factors play a role in this inequality. Women and men have the similar risk for development of ventricular arrhythmias after myocardial infarction, but there are many more gender than sex influences, which cause worse outcome in women. Women suffer more often from conduction disturbances as high-degree atrioventricular blockade as a complication of acute myocardial infarction than men. There is no evident sex or gender difference in cardiogenic shock arrhythmias, but women are at higher risk of cardiogenic shock development.

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Chapter 51

Arrhythmias of subacute phase of myocardial infarction

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Text

Cardiac rhythm or conduction abnormalities have been noted in almost all patients with acute myocardial infarction (AMI) [1].

Several factors contribute to arrhythmogenesis in AMI patients, as myocardial ischemia, hypoxia, myocardial necrosis, altered autonomic tone (increased sympathetic activity or vagal stimulation), metabolic changes (electrolyte and acid-base disturbance), scar formation, and adverse drug effects [2].

Some abnormalities of cardiac rhythm are benign and self-limiting; therefore, they do not need any antiarrhythmic treatment. A "wait and see" strategy, together with the treatment of ischemia and electrolyte imbalances (if present), as well as early administration of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), and statin, has shown to be the best option for the prevention and management of most arrhythmias with no or moderate hemodynamic relevance [2–4].

On contrary, abnormalities of cardiac rhythm require urgent treatment when they (1) compromise myocardial viability by an increase of myocardial oxygen demand (thus enlarging infarct size); (2) impair hemodynamic stability; or (3) predispose to malignant arrhythmias such as ventricular fibrillation (VF) [3].

The majority of malignant arrhythmias occur during the very early phase of the AMI, but they are relevant also during the subacute phase. However, some patients (e.g., those with severely impaired left ventricular function or those with significant residual ischemia) are at high risk of developing malignant arrhythmias even in the long-term. Cardiac arrest secondary to AMI-induced VF occurs commonly without warning signs. Nevertheless, there is evidence that the frequency of malignant ventricular arrhythmias is associated with the extent of underlying infarct area and that aggressive reperfusion protocols with angioplasty or thrombolysis reduces the risk of ventricular arrhythmias and sudden cardiac death (SCD) [4–6].

Mechanisms of arrhythmias during AMI

The pathophysiological abnormalities reported in the early phase of AMI include loss of transmembrane resting potential, modification in refractoriness and excitability, slowing of conduction, and the development of abnormal automatic impulse formation [7–10].

The leading hypothesis for a major mechanism related to malignant ventricular arrhythmias occurring within 30 min after coronary occlusion is microreentry due to loss of homogeneity of electrical characteristics of ischemic myocardium, whereas few hours after coronary occlusion, the pathogenesis of arrhythmias is mainly related to abnormal automaticity [3,7–10]. Prerequisites for reentry include unidirectional block and slow conduction of the cardiac impulse effecting reexcitation. Indeed, after the onset of acute ischemia, and still into the reversible phase of the injury, the acute hypoxia causes a cascade of events into the microcosm of myocardial cells that can be summarized as follow. Acute hypoxia results in an intracellular depletion of ATP and accumulation of ADP and products of anaerobic glycolysis, leading to intracellular acidosis. The intracellular acidosis activates the Na^+/H^+ ion exchange channels resulting in H^+ extrusion in exchange for Na^+ entry. And then, Na^+ are exchanged for Ca^+ (by the activation of the Na^+/Ca^+ exchanger), resulting in intracellular Ca^+ overload and cell swelling [7–10].

The above metabolic changes are accompanied by membrane depolarization due the accumulation of K^+ in the extracellular space, mainly due to reduction of the

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TABLE 51.1 Rhythm disturbances that occur more frequently during the subacute phase of myocardial infarction.

Rhythm disturbance	Causes
Ventricular premature beat	Electrical instability
Ventricular tachycardia	Electrical instability
Ventricular fibrillation	Electrical instability
Accelerated idioventricular beat	Electrical instability
Junctional escape rhythm	Conduction disturbances
Intraventricular block	Conduction disturbances
Atrioventricular block	Conduction disturbances
Sinus tachycardia	Excessive sympathetic activity
Sinus bradycardia	Conduction disturbances
Atrial fibrillation and/or flutter	Excessive sympathetic activity
Paroxysmal supraventricular tachycardia	Excessive sympathetic activity

Na^+/K^+ pump activity and shrinkage of the extracellular space (as a consequence of the cell swelling).

All that led to slowed conduction and altered refractoriness. Of note, the changes in K^+ distribution are far from homogeneous, but they are most pronounced in the center of the infarct. Thus, cells at the center of the ischemic zone have an increase of extracellular K, whereas in the border area (between ischemic zone and normal myocardium) cells are only partially depolarized and have action potentials with a larger amplitude. Slowing of impulse conduction and block occurs in markedly depressed areas leading to arrhythmias such polymorphic VT and VF [3,7–10].

In addition, a sympathetic–vagal unbalance with a relative prevalent sympathetic activity may also represent the trigger of the late unfavorable clinical outcome [7–10]. Table 51.1 summarizes the most frequent abnormalities of cardiac rhythm during the subacute phase of myocardial infarction.

Ventricular abnormalities

Ventricular premature beets

The most common arrhythmia in patients with AMI is the appearance of ventricular premature beats (VPBs). In the acute phase of AMI, almost all patients show VPBs, either alone or organized in couples or short runs, as well as with multiform configuration, or with R-on-T phenomenon (early coupling) [1]. Early studies supported the hypothesis that frequent (more than five per minute) or organized VPBs could pose a serious risk for triggering sustained ventricular tachycardia (VT) and VF [11]. However, recent evidence shows that frequent as well organized VPBs are frequent in many patients who developed VF as well as in those who do not [1,4]. A "wait and see" strategy, together with ischemia treatment and of electrolyte imbalance (if present) correction, is the best approach after an AMI [4]. Early (within 24 h) administration of beta-blockers is associated with a reduction in the occurrence of VF/VT and reduced mortality rates [12–14]. Vice versa, treating VPBs with antiarrhythmic drugs in order to prevent VF may have deleterious effects, due to increased risk of malignant arrhythmias, fatal bradycardia, and asystole [15–17].

The prognostic role of VPBs is uncertain. The Framingham study [18] indicates that post-AMI VPBs may increase the risk of potentially fatal arrhythmias in men but not women. A correlation between the frequency of post-AMI VPBs and fatal arrhythmic episodes was found in men, but not in women, even though women often exhibit an increased risk of in-hospital death compared with men [19–24]. Women could be less prone to developed ventricular arrhythmias. In electrophysiological studies, sex differences have been reported for inducibility of ventricular arrhythmias using electrical stimulation: it is easier to induce ventricular arrhythmias in men with post-AMI scar (95%) than in women (72%) [25,26].

Ventricular malignant arrhythmias

Myocardial ischemia and infarction offer an electrophysiological environment that is particularly favorable to initiation and maintenance of ventricular arrhythmias (see above) [7–10]. VT and VF (Figs. 51.1 and 51.2) account for most of SCD cases that occur before hospital arrival [2,4]. The incidence of VT and VF has declined significantly during the recent decades due to the widespread availability of revascularization therapy (limiting the size of infarction) and to an increased early use of beta-blockers

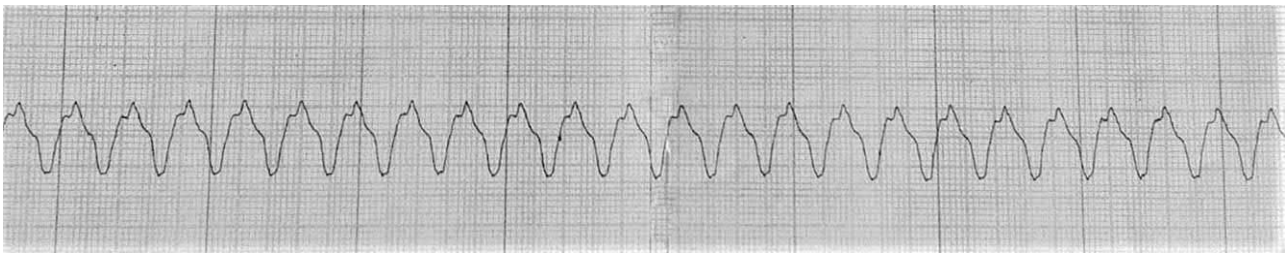

FIGURE 51.1 Monomorphic ventricular tachycardia in lead V1.

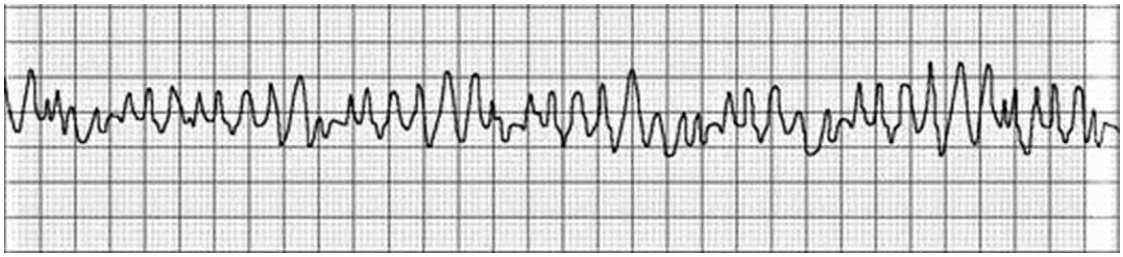

FIGURE 51.2 Ventricular fibrillation: chaotic and irregular deflections of variable morphology and no distinct QRS complexes.

[2,4]. In the prereperfusion era, the incidence of in-hospital VF/VT was ranging from 4% to 40% [8,27]. In the current reperfusion era, the incidence of VF/VT ranges from 3% to 10% in patients treated with thrombolysis [1,28] and from 5% to 6% in patients treated with primary PCI [12]. However, epidemiological studies still show in some countries low rates of reperfusion, mostly due to late (>12 h) hospital arrival, and high rate of unfavorable outcomes [23,29,30].

Incidence: From 5% to 10% of patients develop hemodynamically significant VT or VF during the early hours of in-hospital phase of AMI [31]. The APEX AMI trial (Assessment of Pexelizumab in Acute Myocardial Infarction trial) evaluated the association between sustained VT/VF and its timing on patients presenting for primary PCI. The study found sustained VT/VF occurred in 5.7% of patients. The vast majority (90%) of sustained VT/VF occurred within 48 h of symptoms onset. Of these, 64% occurred before the end of catheterization (early VT/VF) and 26% after the end of cardiac catheterization (late VT/VF) [12].

No difference has been found in the incidence of VT/VF post-AMI between men and women [12,32].

Risk factors for VT/VF: Factors associated with early and late sustained VT/VF in the APEX AMI trial are reported in Table 51.2 [12]. Several other studies had investigated the occurrence of sustained VF/VT to patient characteristics. Among others, the clinical features more frequently reported are Killip classes >1, hypotension, male sex, low preprocedural (TIMI grades flow <1) and postprocedural (TIMI grades flow <3) coronary blood flow, electrolyte disturbances, and ST-segment resolution <70% [12,28,33].

TABLE 51.2 Factors associated with post-AMI sustained VT and VF.

Older age
Heart rate >70 beat/min
Killip class >1
Total baseline ST deviation
Incomplete ST resolution
Hypotension
Low creatinine clearance
Preprocedural TIMI flow grade 0
Postprocedural TIMI flow grade <3
Left ventricular ejection fraction <40%

No significant difference was found in the incidence of VT by AMI location (7.3% in inferior or posterior AMI vs. 7.9% in anterior or lateral AMI, HR = 0.89, $P = .064$), while VF seems slightly more frequent among patients with an anterior or a lateral AMI (9.0% vs. 8.1%, HR = 0.65, $P = .023$) [34].

To determine, in every AMI patient, the risk of malignant ventricular arrhythmias, three vulnerable classes of patients should be considered: (1) patients presenting after a long period of chest pain, (2) patients who have undergone only partial revascularization, and (3) those with a preexisting arrhythmogenic substrate [2–4].

Usually, in textbooks, VF is classified as primary VF, secondary VF, and late VF, accordingly to the clinical setting [3,34]. *Primary VF* occurs unexpectedly in patients with AMI with no sign of heart failure or heart block.

Approximately 40% of primary VF episodes occur within 4 h since the onset of symptoms, 40% from 4 to 12 h, and 20% later. Primary VF accounts for 90% of all prehospital death. Immediate coronary angiography and complete revascularization improved hospital survival in patients with out-of-hospital cardiac arrest with no obvious noncardiac cause of arrest regardless of the ECG pattern [35]. *Secondary VF* is not related to the index ischemic event, but to the anatomical substrates of infarcted myocardium or to ventricular failure and cardiac shock. Generally, it is the final event of a rapid progressive pump dysfunction. *Late VF* develops more than 48 h post-AMI. It usually affects patients with large infarct size [34].

Malignant ventricular arrhythmias seen in the earliest phase of AMI are generally due to reentry, whereas after few hours (>4 h), the mechanism is abnormal automaticity. The vast majority of sustained monomorphic VTs occur late after AMI and arise at the periphery of the site of the necrotic area [10]. At ECG, polymorphic VT is more likely related to ischemia, whereas monomorphic VT ((Fig. 51.1) is more likely related to myocardial scar.

Although women seem less vulnerable to sudden death than men after AMI, as women more frequently than men seek medical attention 12 h after the onset of AMI symptoms [23], there is room to further improve their prognosis.

Symptoms and signs: The severity of symptoms results from VT range from none or mild to cardiovascular collapse and SCD. Although not always present, symptoms and signs include palpitations, symptoms of reduced cardiac output, and hypotension (including diaphoresis, visual disturbances, etc), or congestive heart failure [3]. Most of the time, the clinical presentation is unstable, with frequently fast and polymorphic VT, often degenerating into VF.

Gender differences in the clinical presentation for VT/VF are not described.

Treatment: In case of sustained VT (>30 s), intravenous beta-blockers are recommended if there are no contraindications (such as severe left ventricular dysfunction, pulmonary edema, or shock) [4,20,36–39], as well as correction of electrolyte imbalances (especially hypokalaemia and hypomagnesemia) [2–4,40]. Repetitive electrical cardioversion or defibrillation may be necessary. If there is no sufficient control, i.v. administration of amiodarone is recommended. In case of contraindications to amiodarone, i.v. lidocaine may be considered [4]. Finally, international guidelines recommend immediate coronary angiography and complete revascularization because myocardial ischemia is often the trigger for VT and VF [4,35,40].

Since clinical evidence to support the use of antiarrhythmic drugs has never been completely satisfactory, the invasive approach for treating ventricular arrhythmias has arisen increasingly interest [2]. Transvenous catheter pace termination and/or overdrive pacing should be considered if VT cannot be controlled by repetitive electrical cardioversion [4]. Moreover, radiofrequency catheter ablation at a specialized ablation center followed by implantable cardioverter-defibrillator (ICD) implantation should be considered in patients with recurrent VT, VF, or electrical storm despite complete revascularization and optimal medical therapy [4].

Asymptomatic and hemodynamically irrelevant ventricular arrhythmias should not be treated with antiarrhythmic drugs. Prophylactic treatment with antiarrhythmic drugs is not indicated and may be harmful in increasing the risk of malignant arrhythmias itself as well as of fatal bradycardia and asystole events [3,4,15,16].

VT or VF may also occur at the time of restoration of coronary blood flow (reperfusion arrhythmias). No specific antiarrhythmic drug therapy is necessary due to the benign long-term course [4].

Men and women should be treated in the same way.

Prognosis: The prognostic role of VPBs and VT/VF occurring within the first 48 h of AMI was analyzed in several studies [1,2,4,12,16,18].

In the GUSTO-I trial (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), which enrolled 41,020 patients with STEMI, ventricular arrhythmias occurred in 40,895 (99.7%) patients, while sustained VT, VF, or both occurred in 4188 patients (10.2%) [1]. Therefore, VPBs do not have a prognostic role.

Patients with sustained VT, VF, or both compared with those without these arrhythmias had significantly higher in-hospital and 30-days mortality rates (without substantial difference between in-hospital and 30-day mortality rates). Moreover, patients experiencing both VT and VF had a higher mortality rate (44%) than those with VT alone (18%) or VF alone (24%). At 1-year follow-up, for 30-day survivors, the mortality rate was 7% in those experiencing only sustained VT or both (VT and VF), whereas it was 3% in those experiencing only VF. Therefore, the study showed that after the first 30 days post-AMI, there is a substantial reduction in the risk of death [1]. The study also explored the prognostic role of early (within 2 days from admission) and late (more than 2 days after admission) sustained ventricular arrhythmias. Early compared to late-sustained ventricular arrhythmias were associated with lower mortality rates (43% vs. 57% for VT plus VF, 34% vs. 37% for only VT, and 20% vs. 37% for only VF, respectively) during hospital stay, as well as at 30 day and at 1 year [1].

In the APEX AMI trial, at 90 day, clinical outcome was worse in patients who experienced sustained VT/VF compared to those who did not (mortality rate, 23.2% VT/VF vs. 3.6% sinus rhythm), and among the former, it was worse when sustained VT/VF was late, occurring after primary PCI (mortality rate 33.3%), instead of before the end of cardiac catheterization (mortality rate 17.2%) [19].

Several other studies confirmed that patients with VT/VF have an increased risk of in-hospital and 30-day

mortality [4]. However, recent available data suggest that 30-day survivors do not have a significantly increased of long-term risk of fatal arrhythmic events [41].

Sustained VT or VF rising after 48 h of AMI onset is usually not triggered by recurrent ischemia and is associated with an increased risk of arrhythmic death. These patients should be reevaluated, for primary prevention of SCD by ICD implantation, 6−12 weeks after revascularization. Those with preexisting impaired left ventricular function may be considered for ICD implantation for primary prevention even within the early postinfarction period [2,4,42].

Finally, it is important to highlight that despite complete revascularization and treatment with antiarrhythmic drugs, there are some patients who may develop persistent VT. For these patients, 2017 European Society of Cardiology guideline suggests that overdrive stimulation may help to control the situation, but often recurrence of VT/VF upon cessation of stimulation occurs; therefore, radiofrequency ablation of such triggers appears to be the only treatment option, especially when more than three episodes of VT or VF occur in any 24-h period [2,4,42,43].

The absolute risk of SCD following AMI is greatest in the early period after myocardial infarction and among patients with the lowest ejection fraction and declines significantly over time, reaching a steady state at approximately 1 year [44,45]. The MADIT-II trial included patients with prior MI and left ventricular ejection fraction (LVEF) < 30% and showed a 30% reduction in the adjusted hazard of SCD with ICD therapy at nearly 2-year follow-up [46]. According to the abovementioned concept, prophylactic implantation of a defibrillator improves survival and should be considered as a recommended therapy as shown by the MADIT-II trial [2,4,40,46]. Recently, use of a wearable cardioverter-defibrillator (WCD) in the immediate post-AMI period (40−90 days) has been proposed as a bridge to ICD implantation in patients who are at significant risk for VT/VF but are not immediate candidates for ICD implantation or have an acute contraindication to ICD implantation such as infection. Nevertheless, the Vest Prevention of Early Sudden Death Trial (VEST) did not find any significant difference in the primary endpoint of sudden death or death from ventricular tachyarrhythmia at 90 days between the WCD in addition to optimal medical management− and optimal medical management−alone (control) groups (1.6 vs. 2.4%) [44]. As a result, routine use of WCD remains unclear.

In the intermediate and long-term follow-up post-AMI, the mortality rate for sudden death is greater for men then for women. In the VALIANT study, during 2 years of follow-up of 14,703 patients with heart failure and ventricular dysfunction after AMI, there were 1067 (7.3%) cases of SCD. Of these, 67% occurred in men and 33% in women [44]. The Framingham Study [18], which prospectively examines a cohort of 2873 women for evaluating the development of sudden death, found that in women with coronary artery disease, the risk of sudden death was half as high as in men with coronary artery disease. Ten years after AMI, the rate of sudden death was 5.3% in women and 11.9% in men [18].

Supraventricular abnormalities

Sinus bradycardia

Sinus bradycardia is common in the first hours of inferior MI (Fig. 51.3). It often requires no treatment. But, if

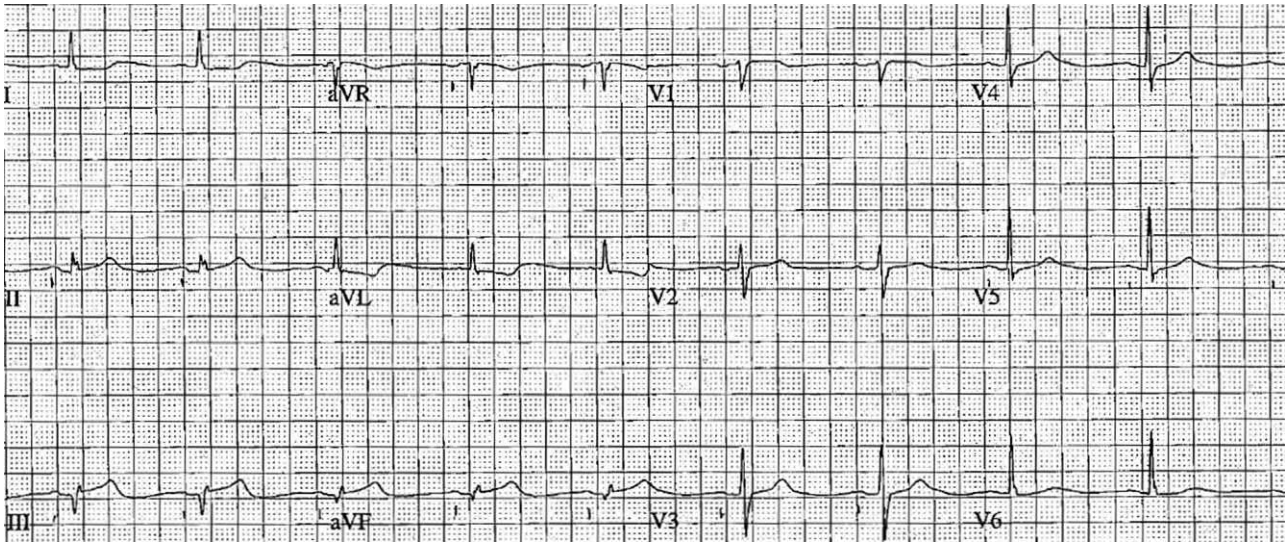

FIGURE 51.3 Sinus bradycardia (57 bpm) in a patient with inferior acute myocardial infarction.

accompanied by severe hypotension, sinus bradycardia should be treated with i.v. atropine [4]. Severe bradycardia occurs more often in women than men (22% vs. 5%) after abrupt coronary occlusion [47].

Sinus tachycardia

Sinus tachycardia is found in about 30% of patients, especially those with anterior AMI. Mechanism of sinus tachycardia is related to the physiological-reflex response to left ventricular dysfunction and to increased activity of sympathetic nervous system due to various factors like pain, anxiety, left ventricular failure, and catecholamine release. Sinus tachycardia has detrimental effects in patients with AMI, thus results in an increase of oxygen consumption, adversely affecting the ischemic myocardium. In patients with AMI, the optimal rate is in the range of 60–80 beats/min [3]. Adequate rate control can be accomplished by administration of beta-blockers, if not contraindicated, as in those patients in whom the sinus tachycardia is a manifestation of hypovolemia or ventricular failure.

Atrial premature contractions and paroxysmal supraventricular tachycardia

Atrial premature contractions are rather common, occurring in approximately half of all patients with AMI. Several time atrial premature contractions are organized in run of paroxysmal supraventricular tachycardia that has negative effects due to consequent rapid ventricular contraction and elevation of myocardial oxygen consumption. Most of the time, restoration of sinus rhythm can be achieved by augmentation of vagal tone by manual carotid stimulation [3].

Atrial fibrillation

Atrial fibrillation is the most frequent supraventricular tachyarrhythmia (Figs. 51.4–51.7). The widespread use of PCI during the acute phase of AMI has determined a notable decline in AF incidence. However, it still affects from 2.3% to 22% of patients with AMI [48,49]. Several studies have suggested that new-onset AF may be reduced by beta-blockers, ACE inhibitors/ARBs, and also early onset statin therapy [48]. New-onset AF occurs more

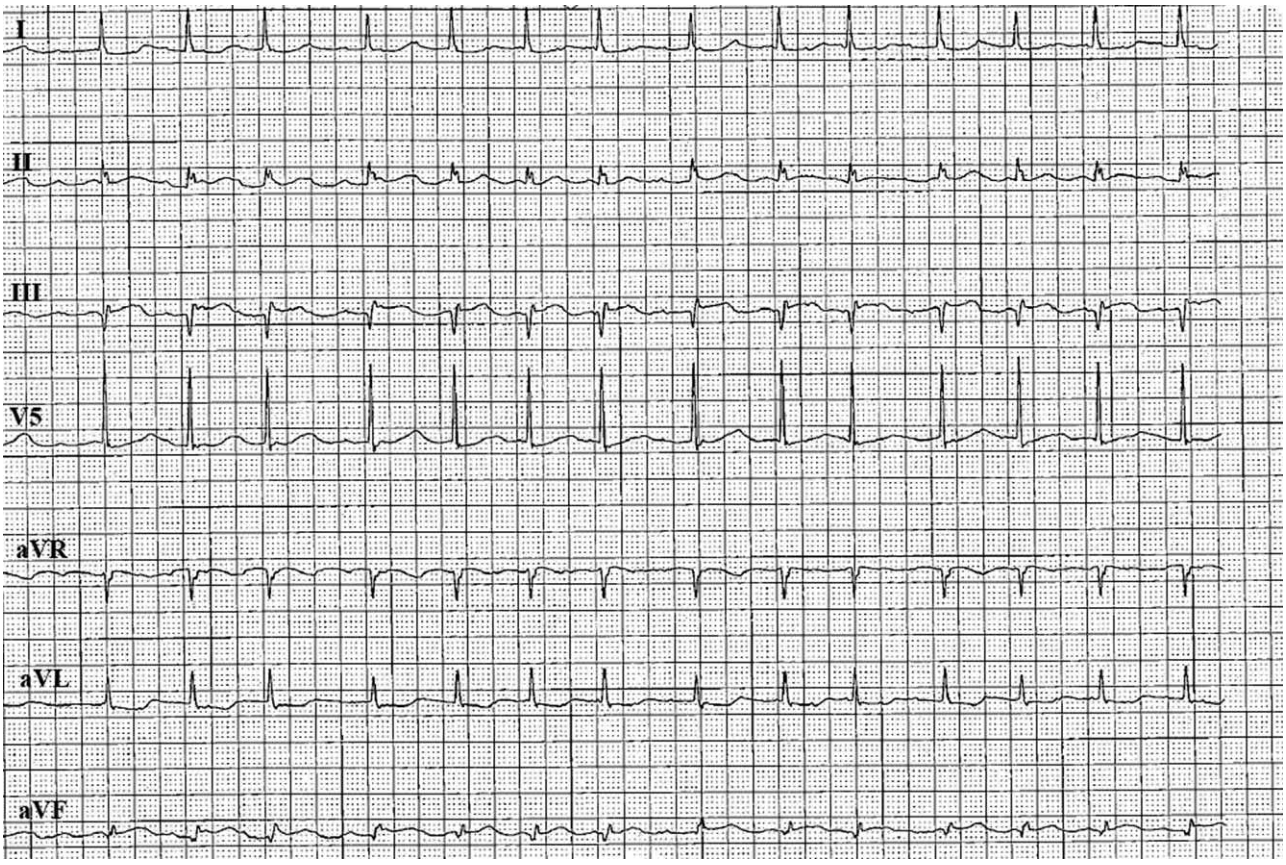

FIGURE 51.4 Atrial fibrillation during the acute phase of inferior myocardial infarction.

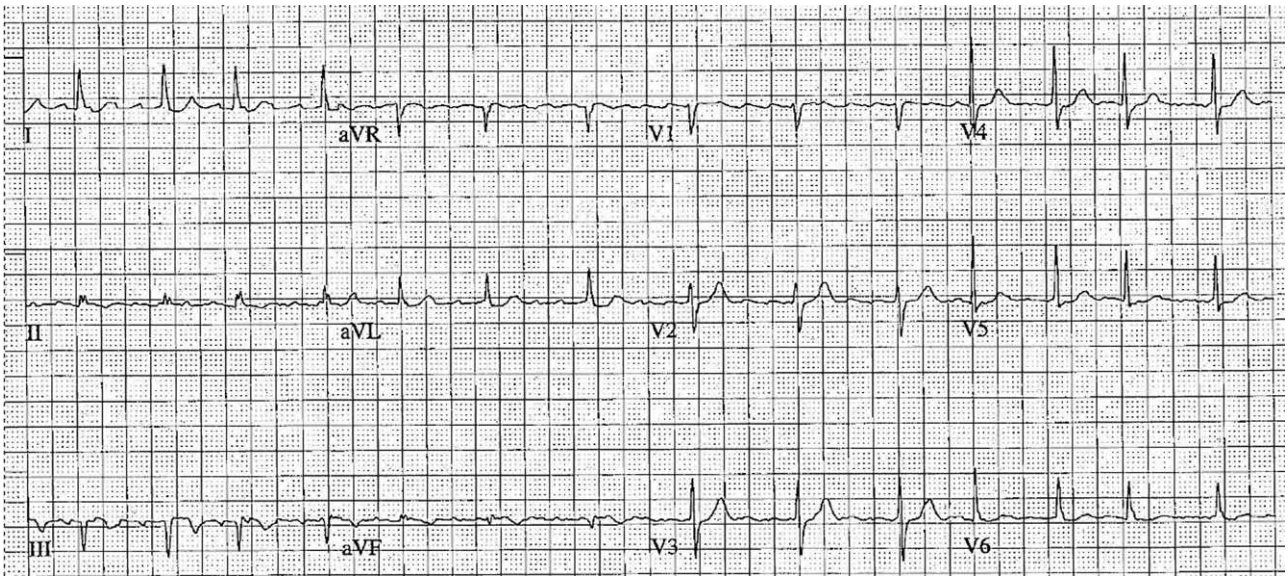

FIGURE 51.5 Atrial fibrillation during the subacute phase of inferior myocardial infarction.

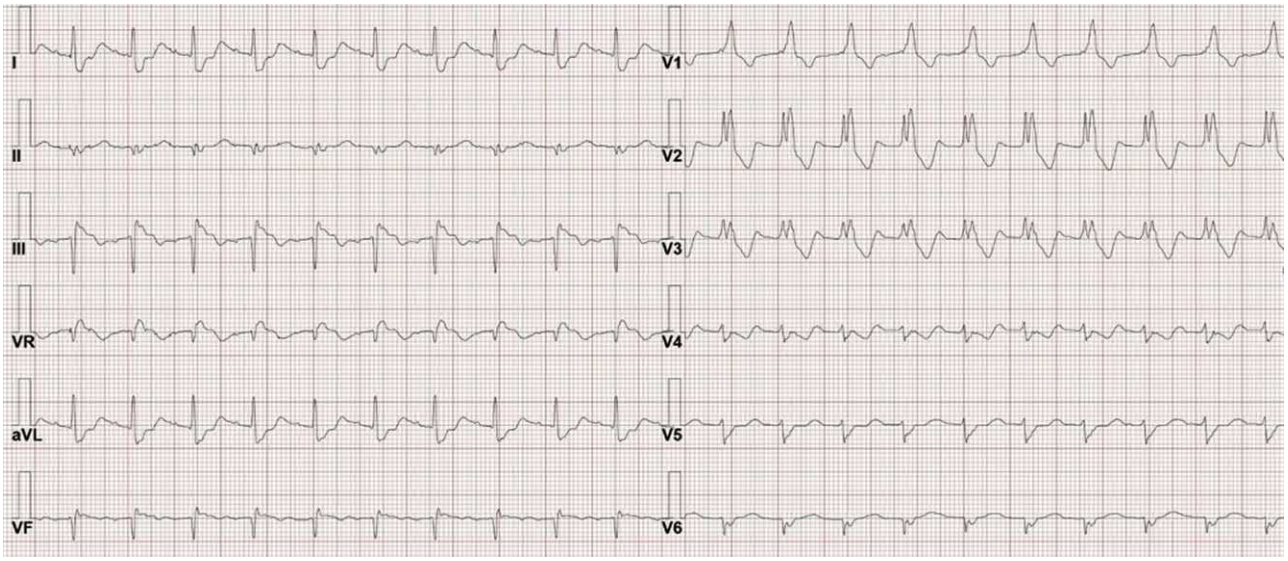

FIGURE 51.6 Atrial fibrilloflutter with high ventricular rate and right bundle branch block during the subacute phase of myocardial infarction.

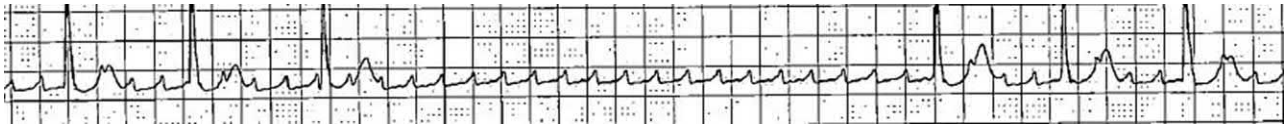

FIGURE 51.7 Atrial fibrilloflutter in a patient with acute myocardial infarction: night ECG monitoring documented a pause of 4 s.

frequently following anterior than inferior AMI, as a consequence of left atrial ischemia.

Female gender and age >70 years are significantly predictors of AF after AMI [48].

In many cases, the arrhythmia is well tolerated, and no specific treatment is required, other than anticoagulation [4,50]. However, sometimes the loss of atrial contribution to ventricular filling may result in significant reduction of cardiac output. Indeed, in patients without AMI, loss of atrial systole usually decreases the ventricular output by 15%–20%, while in AMI patients (as in all patients with

diastolic dysfunction), loss of atrial systole may decrease the ventricular output up to 35% [3,51].

The management of AF is largely based on symptoms and sign of hemodynamic instability. Immediate treatment by electrical cardioversion or antiarrhythmic drug is required in case of hemodynamic instability. While, in case of hemodynamic stable patients, there is scarce information indicating preferences for rate control over rhythm control in patients with AF and recent AMI [52]. Acute rhythm control with antiarrhythmic drugs is limited to the use of amiodarone [4,48,50]. Adequate rate control can be accomplished by administration of beta-blockers or i.v. digoxin in patients with severe LV dysfunction [2,4,52].

AF in patients with AMI is a negative prognostic factor. STEMI patients with documented AF have worse short- and long-term prognoses when compared with patients in sinus rhythm [53,54]. AF is associated with a higher mortality, reinfarction, stroke, cardiogenic shock, and heart failure [55,56]. In the Swedish registries, AF was documented in 24,023 over 155,071 (15.5%) patients. At 90-day postdischarge, there was no difference in patient's outcome among those with de novo AF (with and without sinus rhythm at discharge), paroxysmal AF, and chronic AF, been all AF patients at an increased risk of events compare to those without AF, been the former at the double risk of events (mortality, reinfarction, and stroke) [53]. Of note, also transient, self-terminating AF during STEMI relates to a significantly higher rate of events during long-term follow-up [48,53].

AF gives an increased risk of events even when it develops more than 30 days post-AMI [54]. In the study of Jabre et al., AMI patients were grouped in five classes: (1) sinus rhythm, (2) AF before AMI, (3) AF new onset within 2-day post-AMI, (4) AF new onset between 3- and 30-day post-AMI, and (5) AF new onset >30 days post-AMI. During a mean follow-up of 6.6 years, 1638 deaths occurred. AF was associated with an increased risk of death. This risk differed markedly according to the timing of AF and was the greatest for AF occurring >30 days post-AMI [54].

The CARISMA study, using an implantable cardiac monitor, revealed that the incidence of AF after AMI in patients with LVEF<40% is approximately 30% (much more than previously though). The risk of new-onset AF is highest during the first 2 months after the AMI (16% event rate) and decreases until month 12 post-AMI, after which the risk for new-onset AF is stable [55]. The strongest clinical factors associated with mortality in patients with atrial fibrillation post-AMI are heart failure, Killip Class IV, and older age [48].

AF requires oral anticoagulant therapy to prevent thromboembolic complications (particularly stroke); however, this treatment exposes patients to an increased risk for future bleeding events, which is higher for women then for men.

Conduction disturbances

Myocardial ischemia can produce conduction disturbances at any level of the conduction system. Like ventricular arrhythmias and atrial fibrillation, conduction disturbances also decreased from prereperfusion era to thrombolytic therapy (incidence 5%−10%) and primary PCI (incidence 4%) [34,57,58]. Atrioventricular (AV) blocks and interventricular conductions defects occur especially in inferior/posterior STEMI [34]. These blocks may arise in the AV node (causing various degree of AV blocks), in main bundle branch (causing left or right bundle branch block), and in the anterior or posterior division of the left bundle (causing anterior or posterior fascicular block).

No significant statistical correlation was found between the incidence of heart blocks and the age or sex of patients [59].

Atrioventricular block

First-degree AV block occurs in <1.5% of patients with AMI admitted to hospital. Generally, it does not require specific treatment. If it is associated with signs of excessive vagal tone (i.e., severe hypotension), administration of atropine may be helpful.

Second-degree AV type I block (Mobitz I or Wenckebach) occurs also in <1.5% of patients with AMI admitted to hospital. It is usually associated with inferior wall AMI due to occlusion of the right coronary artery. AV block associated with inferior wall infarction is usually supra-Hisian and usually resolves spontaneously or after reperfusion [57]. Only very seldom second-degree AV type I block causes adverse hemodynamic effects. If so, atropine should be used first; if it fails, pacing should be instituted. Agents that slow AV conduction (such as beta-blockers, digitalis, verapamil, or amiodarone) should be used with caution. Second-degree AV type I block does not appear to affect survival [3,4,34].

Second-degree AV type II block (Mobitz II) is rare (<1% of patients with AMI admitted to hospital).

Several times, it is associated with a wide QRS complex suggesting a lesion in the conduction system below the bundle of His, which may progress suddenly to complete AV block. Temporary demand pacemaker is the suggested treatment [57].

Third-degree AV block (complete AV block) occurs in roughly 4% of patients with AMI admitted to hospital [34]. Because the conduction system received blood either from the AV branch of right coronary artery or the septal perforating branch of left anterior descending coronary artery, third-degree AV block may occur either with inferior or anterior AMI.

In case of inferior wall AMI, it usually develops gradually from a first-degree or type I second-degree AV block; the escape rhythm is generally a stable junctional rhythm

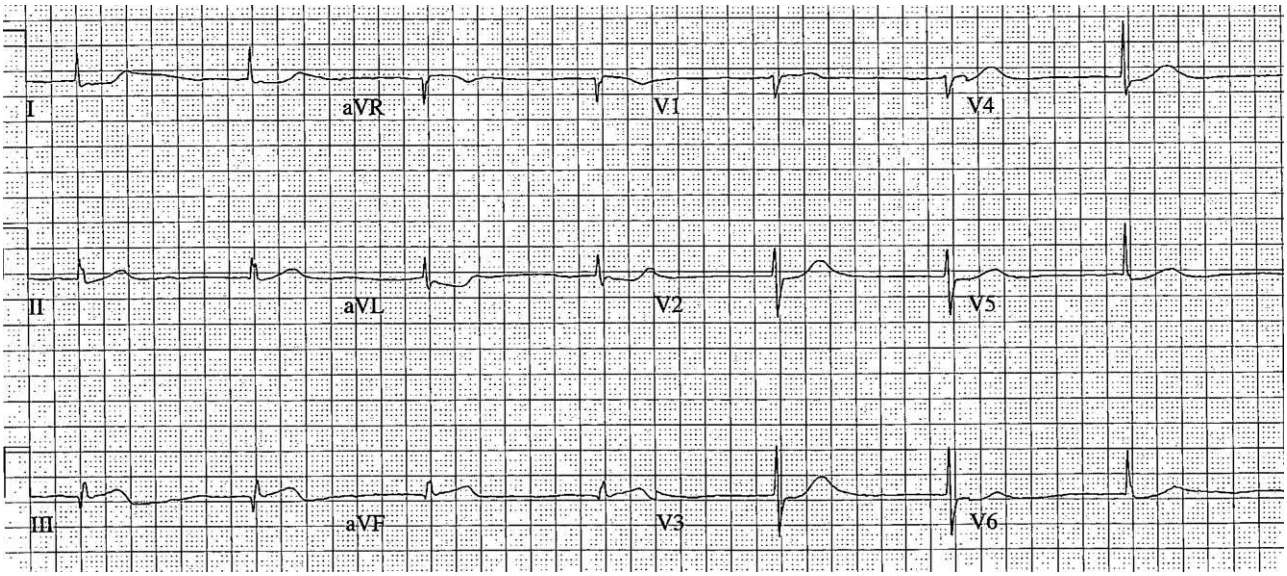

FIGURE 51.8 Junctional rhythm in a patient with inferior acute myocardial infarction.

TABLE 51.3 Conduction blocks of His bundle related to acute coronary occlusion.

Fascicles of the his-purkinje	Blood supply	Intraventricular blocks
Anterior division of left bundle	Septal perforators (from LAD)	Left anterior division block
Posterior division of left bundle	LAD and RCA	Left posterior division block
Right bundle	LAD and RCA	Right bundle branch block

LAD, left anterior descending; *RCA,* right coronary artery.

(narrow QRS at >40 bpm); it spontaneously resolves after few days (Fig. 51.8).

In case of anterior wall AMI, it usually appears suddenly (although often preceded by Mobitz II) in 12−24 h after AMI symptom onset, and it is generally the consequence of extensive necrosis involving also the septum; the ventricular escape rhythm (generally <40 bpm) is unstable, thus frequently results in ventricular asystole; the mortality rate is very high (>70%), resulting in severe ventricular dysfunction.

AV sequential pacing should be considered in patients with complete AV block, RV infarction, and hemodynamic compromise [4]. Revascularization should be considered in patients with AV block who have not yet received reperfusion therapy (e.g., late arrival) [4].

Intraventricular block

Intraventricular conduction disturbances occur in about 5% of patients with AMI, but almost half are already present at the time of first ECG [3]. The development of a new bundle branch block or hemiblock usually indicates extensive anterior AMI (Table 51.3). Patients with intraventricular conduction defects account for the majority of patients who develop VF during hospital stay [60]. A transvenous pacing electrode should be inserted in the presence of advanced AV block with a low escape rhythm and if bifascicular or trifascicular block develops [55].

Conclusion

Reperfusion treatments have significantly reduced the incidence of AMI related arrhythmias, both in women and men.

Regarding malignant ventricular arrhythmias, in the literature, there are no differences between men and women in their incidence. However, it should be noted that VT/VF is related to time of ischemia (among other factors) and time from symptom onset to hospital arrival is greater in women than men. Therefore, two considerations should be done. First, in literature, the number of women with early VT/VF could be underestimated (due to episodes of sudden death before hospital arrival). Second, even an earlier hospital arrival could rise reports on the number of VT/VT

in female gender, which could also improve women outcome. In the intermediate and long-term follow-up, post-AMI women seem less vulnerable to sudden death than men but have more heart failure. Regarding supraventricular abnormalities, women more frequently than men have severe bradycardia and AF.

Men and women should be treated in the same way.

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Chapter 52

Sex-specific arrhythmia risk of post-MI follow-up

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Introduction

Investigating the question of sex-specific arrhythmia risk following an acute myocardial infarction (AMI) cannot be properly done without considering sex differences in post-MI patients in general first. It is of interest to discover the unique features of men and women that lead to those differences to close the sex gap [1]. As early as 1979, the Minnesota Heart Survey investigated whether or not sex influenced outcome after AMI. In an investigation from 1995, they discovered that female sex was prognostic for a poorer outcome with a higher mortality after AMI [2].

Progress in drug and interventional treatment of coronary artery disease (CAD) and AMI has led to an improvement in cardiovascular mortality over the past two decades. This trend is equally evident for men and women [3]. The recognition that mortality, especially after AMI, varies between men and women has led to more intensive research in this area, and the results of landmark randomized clinical trials have contributed to improved cardiovascular care in women [4,5].

However, CAD in women remains underobserved, underdiagnosed, and undertreated. In the United States, annual CAD mortality has remained higher in women than in men.

Sex-specific CAD research over the last two decades has led to a better understanding and important insights into the sex-specific pathophysiology of coronary heart disease in women. Women are almost 10 years older than men at the time of their first myocardial infarction, have more comorbidities, in particular they more frequently suffer from diabetes mellitus and hypertension, and less frequently have a severe obstructive disease of their epicardial coronary arteries, but rather show microangiopathic changes which are not accessible for catheter intervention [6,7]. Several studies have shown that women with acute coronary syndrome are less likely to be treated with guideline-driven medical therapies [8−10], less likely to receive a cardiac catheterization [8−11], and less likely to receive timely reperfusion therapy [9,10,12−16].

Some authors [17−19] postulate age difference as a major risk factor for excess mortality in women after AMI. Thus, the results of the Valiant study showed no difference in short- and long-term mortality between men and women in over 4500 female postinfarction patients after adjustment to age, comorbidities, and other clinical covariables. However, more women than men, regardless of the extent of left ventricular systolic dysfunction or remodeling, developed long-term heart failure [17].

In 2017, Ubrich et al. [18] also found similar results in 3840 consecutive AMI survivors (994 females, 2846 males), namely that women who suffer a heart attack are older, suffered more frequently from hypertension and diabetes mellitus. Looking at the entire cohort, women showed increased mortality with a hazard ratio (HR) of 1.54 compared to men ($P < .0001$). To exclude the influence of age, different comorbidities, left ventricular ejection fraction (LVEF), cardiovascular risk factors, and type of revascularization, a 1:1 case matching was performed. A male counterpart was found for 802 of the female patients, but there was no corresponding male match for 192 (19%) female patients. In the matched cohort, there was no difference in overall mortality for men and women during the 5-year long-term follow-up (see Fig. 52.1).

However, looking at the first-year follow-up, female patients showed significantly higher mortality (HR 1.61; $P = .045$) as you can see in Fig. 52.2A, while mortality was almost identical for both sexes between years 2 and 5 (HR 0.93; $P = .693$), as you can see in Fig. 52.2B.

Reasons for the increased mortality of women within the first year remain unclear; the matching criteria can be excluded as causes. The authors therefore suggest following female AMI patients more closely the first year after the event.

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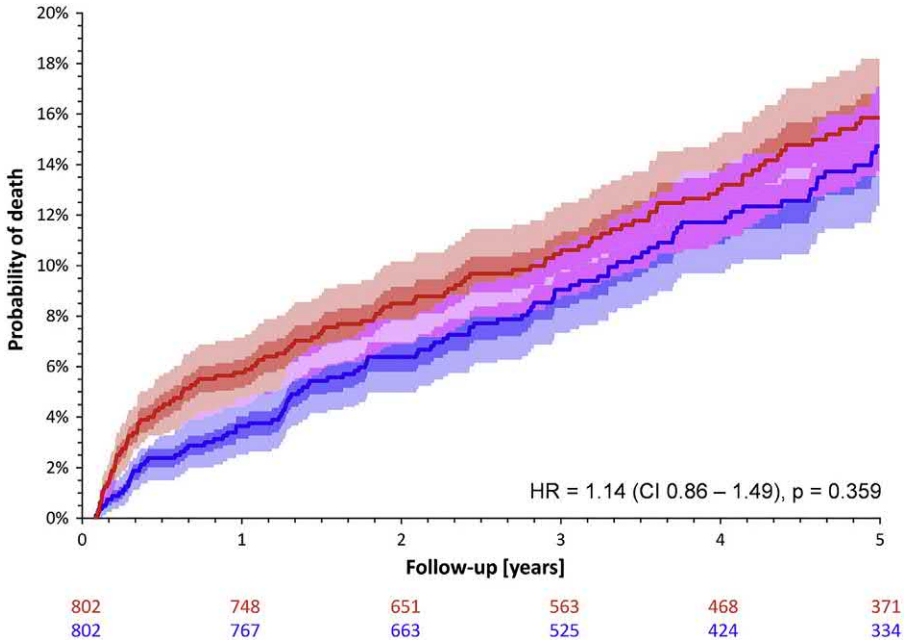

FIGURE 52.1 Probabilities of death stratified by sex in the cohort of matched patients. Red and *blue lines* and bands correspond to females and males, respectively. The *dark-shaded and light-shaded areas* correspond to interquartile bands and 90% confidence bands of the Kaplan–Meier probability curves, respectively. Numbers of patients at risk are shown below the graph in colors corresponding to the probability curves. CI—95% confidence interval; HR—hazard ratio of females vs. males. From *Ubrich R, Barthel P, Haller B, Hnatkova K, Huster KM, Steger A, et al. Sex differences in long-term mortality among acute myocardial infarction patients: results from the ISAR-RISK and ART studies. PLoS One. 2017;12(10):e0186783.*

The 192 female patients for whom no male match could be found differed significantly from the matched ones. They were significantly older and suffered more frequently from diabetes mellitus and high blood pressure. They had significantly less frequent obstructive CAD and the rate of revascularization by PCI was remarkably lower in unmatched women compared to matched women. The survival of unmatched women was also significantly worse than that of matched women (5-year mortality of 34.4% vs. 13.6%; HR = 2.89; $P < .0001$).

Arrhythmias after AMI

Coronary or ischemic heart disease is the most common form of structural heart disease worldwide [20]. The proportion of men is significantly higher than that of women. For this reason, women are often underrepresented in studies on sex-specific differences in the incidence of ventricular arrhythmias in patients with coronary heart disease and there are little data available [21].

Patients who have survived an acute heart attack are at risk of sudden cardiac death (SCD) subsequently. About 50% of all cardiovascular deaths after a survived heart attack are SCDs. Epidemiological studies on SCD and sudden cardiac arrest (SCA) have shown that the predominant mechanism behind the SCD event is a ventricular arrhythmia associated with the underlying CAD [22].

Recent data from the Framingham Heart study [22] showed that the remaining lifetime risk of SCD for the remaining lifetime of men was at least twice as high for all index ages (45, 55, 65, and 75 years) as for women. Men had a similar lifetime risk at index ages 45, 55, and 65, with estimates ranging from 10.1% to 11.2%. Women also had a similar residual lifetime risk of SCD for all index ages, between 2.4% and 3.4%. The majority of SCD events occurred before the age of 70.

In 1996, Albert et al. [23] have shown in a study of 335 patients with survived cardiac arrest that women were less likely than men to have underlying coronary heart disease (45% vs. 80%), see Fig. 52.3. The underlying structural heart disease in women was significantly more heterogeneous and in 10% no structural heart disease was found.

Autopsy studies have also shown that women who die due to SCD are less likely than men to suffer from ischemic heart disease. This was also confirmed by a recently published large Finnish study [24]. More than 5800 SCD victims were examined, 80% were men and 20% women. Although ischemic heart disease was the most common cause (71.7% in women and 75.7% in men, $P = .005$) in both sexes, women were more likely to have a nonischemic cause. In other autopsy studies on SCD, the prevalence of coronary heart disease was significantly lower. In the recently published WISE study, the proportion of female SCD victims with obstructive CAD was only 27%

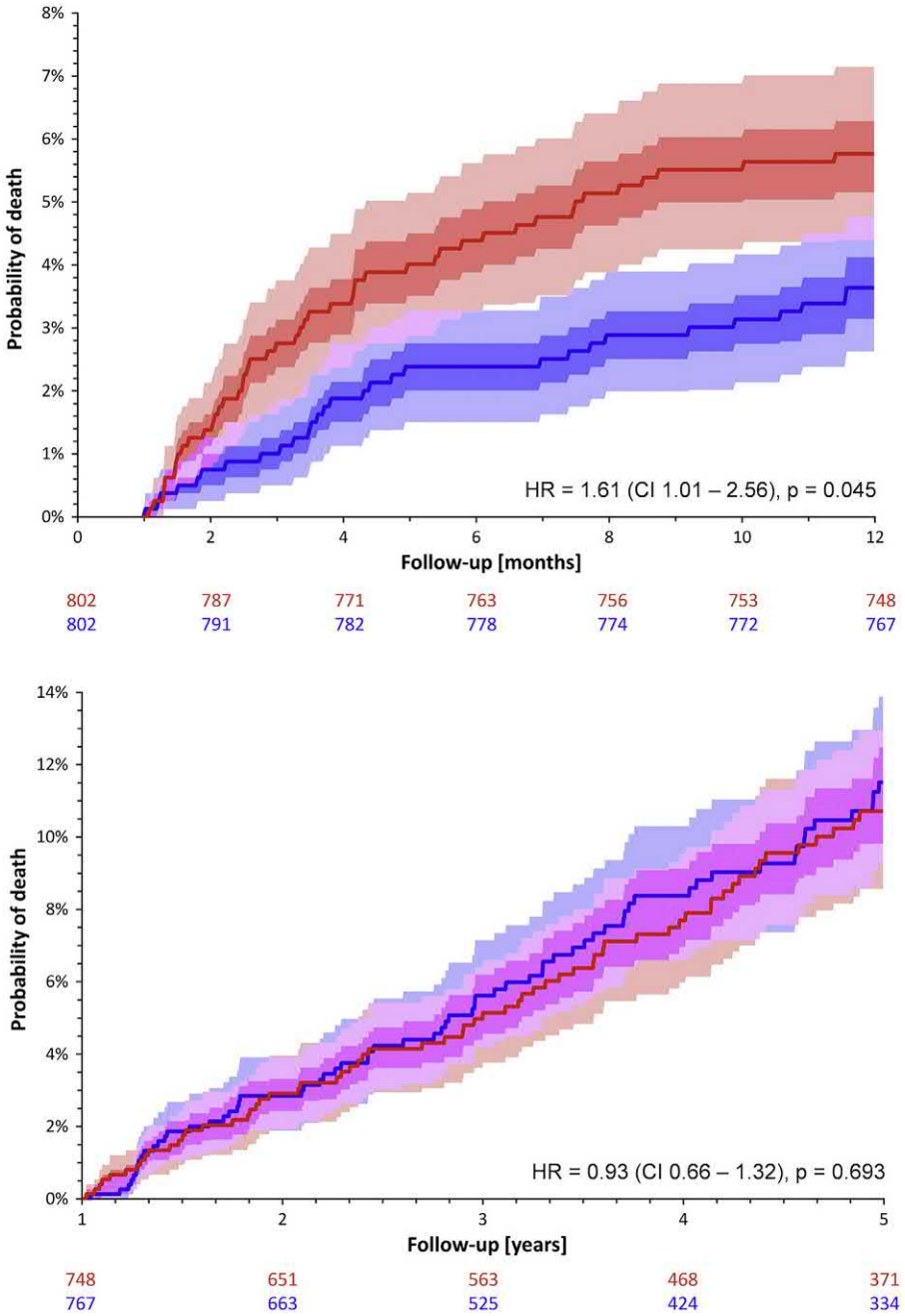

FIGURE 52.2 (A) Probabilities of death stratified by sex in the sex-matched cohort during the first year after the index infarction. (B) Probabilities of death stratified by sex in the sex-matched cohort between the second and fifth year after the index infarction. From *Ubrich R, Barthel P, Haller B, Hnatkova K, Huster KM, Steger A, et al. Sex differences in long-term mortality among acute myocardial infarction patients: results from the ISAR-RISK and ART studies. PLoS One. 2017;12(10):e0186783.*

compared to those without or with minimal CAD (57%; 17% lacked information) [25].

The fact that women are less "susceptible" to persistent ventricular tachycardia or ventricular fibrillation has been shown in several studies which reported that VT/VF in the EPU can be triggered less frequently in women after infarction.

In a 1991 study, Vaitkus et al. [26] investigated whether there was a difference in the inducibility of ventricular arrhythmias between men and women who suffered from coronary heart disease and had survived SCA. It was found that the probability of inducing ventricular arrhythmias in men was about twice as high as in women (73% vs. 39%). The reason for this difference has not yet been sufficiently

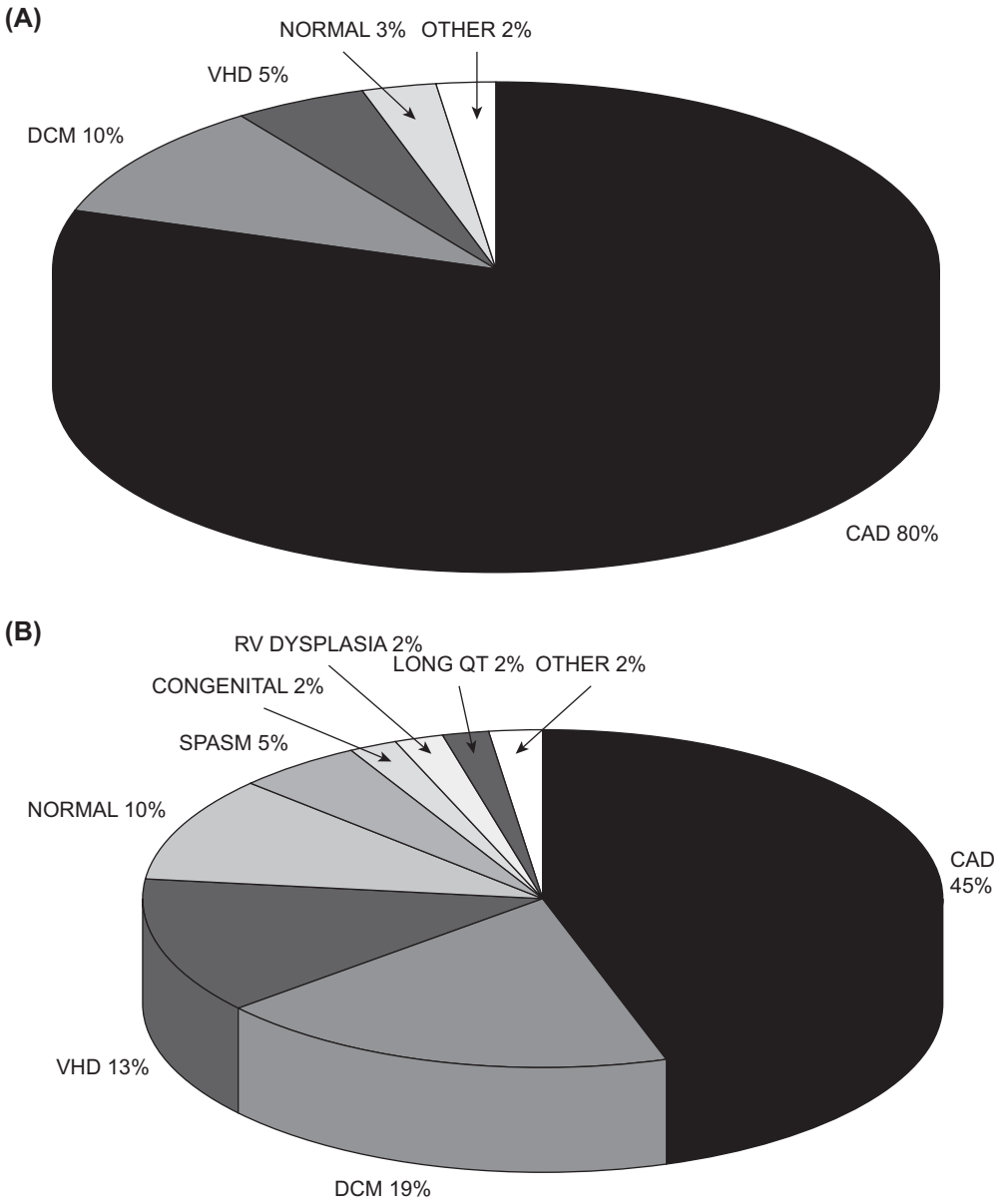

FIGURE 52.3 Pie chart illustrating the proportions of various types of underlying structural heart disease in the male (A) and in the female (B) survivors of cardiac arrest. CAD indicates coronary artery disease; *DCM*, dilated cardiomyopathy; *RV*, right ventricular; *SPASM*, coronary vasospasm; and *VHD*, valvular heart disease. From *Albert CM, McGovern BA, Newell JB, Ruskin JN. Sex differences in cardiac arrest survivors. Circulation. 1996;93(6):1170–1176; Reproduced with Permission of the publisher Wolters Kluwer Health, Inc. Circulation 1996;93(6):1170–6.*

clarified. The authors concluded at that time: "The finding of less frequent inducibility of ventricular tachycardia or ventricular fibrillation in female survivors of cardiac arrest is not explained by differences in electrophysiologic substrate, emphasizing our imperfect understanding of the pathophysiology of sudden death and calling into question the validity of applying a uniform strategy of management for both men and women with cardiac arrest."

Results from studies on primary prophylactic ICD implantation to prevent SCD confirm these early findings. All ICD studies consistently showed that women with ischemic cardiomyopathy have fewer ventricular arrhythmias than men, as measured by a lower risk of adequate ICD therapy due to VTs/VF [27–34]. In the MUSTT study [31], women who had suffered a heart attack were less prone to sustained ventricular arrhythmias, older, more prone to heart failure, and more recent heart attacks than men.

These observations were confirmed in a recently published post-hoc analysis of the MADIT-CRT study [33]. Women with CAD had a 49% lower risk (HR 0.51 (0.33–0.79); $P = .003$) of getting VT/VF or dying compared to men.

The 3-year probability of developing VT/VF or dying derived by Kaplan–Meier was significantly lower in women with ischemic heart disease and ICD implantation than in men (21% vs. 35%; $P = .033$), see Fig. 52.4, while no significant difference between men and women was observed in patients with nonischemic heart disease (21% vs. 32%; $P = .220$). In general, the cumulative incidence of VT/VF was significantly lower in women than in men.

Women with ischemic heart disease and LBBB who received CRT-D benefited most. They had the lowest incidence of VT/VF or death compared to men. Mortality reduction in this study was significant for both sexes.

In contrast, mortality in women in most other prophylactic ICD implantation studies [27,30,35] could not be significantly reduced, unlike in men who showed a highly significant reduction in mortality. However, the proportion of women in these studies was only 16%–33%, so the nonsignificant outcome may be due to a statistical problem [36].

The RAFT study [37] also showed that women benefited significantly more from the implantation of a CRT-D device, with a 48% reduction in the endpoint of death or hospitalization due to heart failure.

The underlying causes of women's reduced susceptibility to sustained ventricular tachycardia or ventricular fibrillation are still unknown, even almost 30 years after the first publications in the early 1990s. Possible reasons discussed are sex-specific differences related to the hormone status in autonomic tone, ventricular repolarization, cardiac ion channel function, and intracellular calcium handling [38–44].

Risk stratification

A challenge not yet satisfactorily solved after a myocardial infarction is the identification of patients who later suffer from malignant cardiac arrhythmias and die from them. As already mentioned, up to 50% of all cardiovascular deaths

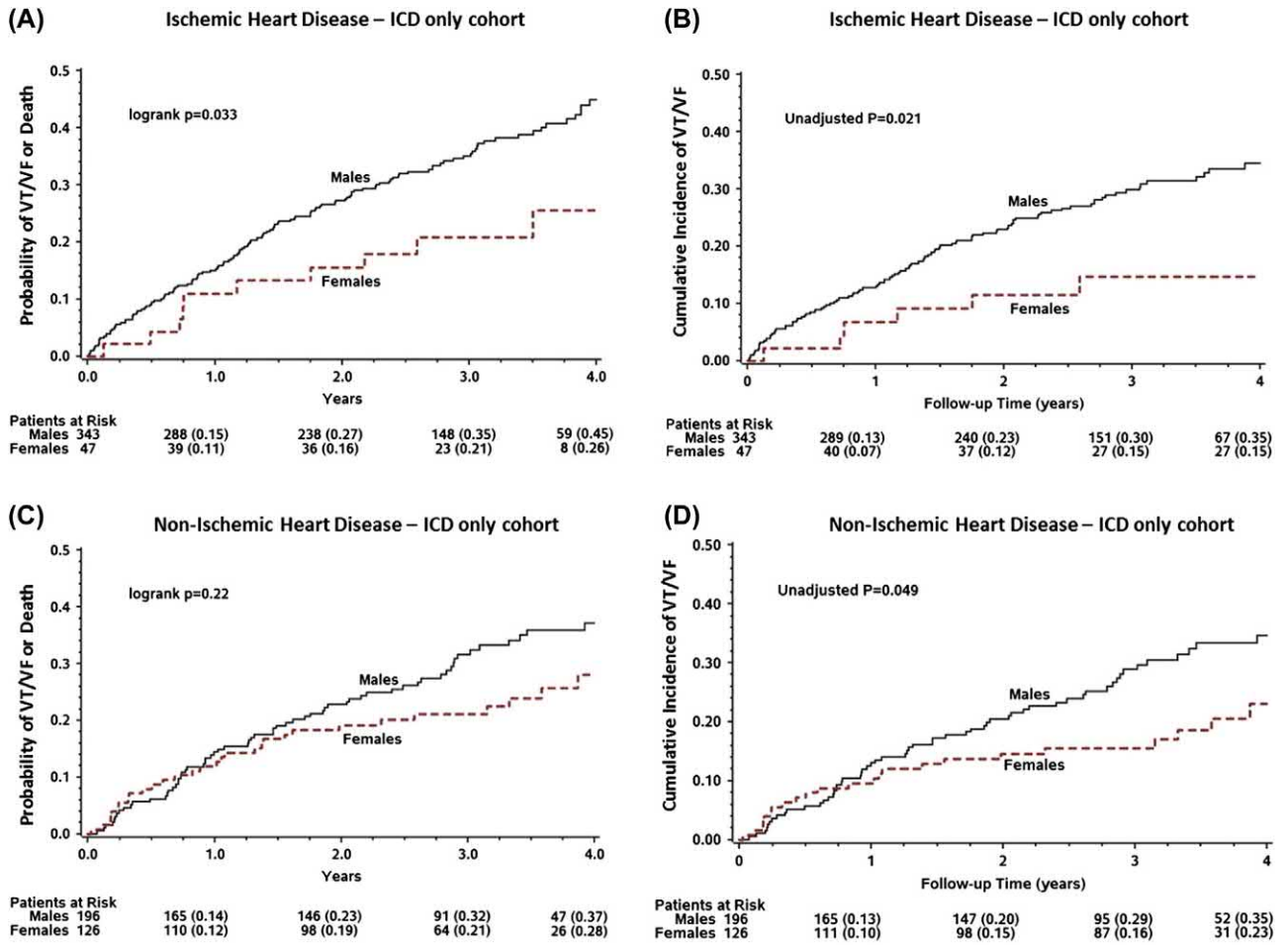

FIGURE 52.4 Kaplan–Meier curves of the probability of VT/VF or death and cumulative incidence of VT/VF based on sex and etiology of structural heart disease (i.e., ischemic vs. nonischemic). From *Tompkins CM, Kutyifa V, Arshad A, McNitt S, Polonsky B, Wang PJ, et al. Sex differences in device therapies for ventricular arrhythmias or death in the multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy (MADIT-CRT) trial. J Cardiovasc Electrophysiol. 2015;26(8):862–871. Reproduced with Permission of the publisher John Wiley and Sons.*

in patients with coronary heart disease are SCDs that may be prevented by implantation of an ICD. Since the publication of the MADIT study [30,45], the only criterion for a prophylactic ICD implantation is an LVEF of <35%. The treatment of AMI at that time differs significantly from acute treatment today. At that time, acute reperfusion therapy using lysis or even catheter intervention was not common.

Fortunately, the percentage of patients who have a highly restricted LVEF (below 35%) is significantly lower in a modern treated patient population. Furthermore, it is known from large epidemiological studies that most patients suffering from SCD after AMI have an LV function >35% [46,47]. For this reason, scientific groups worldwide are working to find risk parameters for patients after an AMI that indicate an increased mortality risk, regardless of the LV function, both for a fatal rhythm event or for the development of heart failure.

Some of these parameters quantify a disturbed autonomic function, such as heart rate variability [48–54], heart rate turbulence [55–61], deceleration capacity [56,62], and baroreflex sensitivity [63–66]. Other parameters identified inhomogeneous electrical de- or repolarization as risk indicators, such as prolonged QT time [67–70], T-wave alternans [71–73], or QRS-T angle [74–77].

The parameters were developed and validated on large postinfarct collectives. The proportion of women in all these collectives is about a quarter of the patients. There are little data on whether these risk indicators are equally valid for women and men. There are no prospective investigations on this and only a few studies on whether women and men differ in the extent of these parameters. In addition, there is the previously mentioned age difference between men and women who suffer a myocardial infarction.

It is known that autonomic cardiovascular regulation is subject to an aging process and that there are differences between men and women that are most likely to be hormonal.

For example, middle-aged women physiologically have a higher resting heart rate than men of the same age [78–82] but this difference decreases with increasing age [79,82,83]. Similar differences have been made for HRV parameters, both in the time domain and in the frequency domain. Women have lower SDNN, RMSSD values, lower LF/HF ratio, and lower LF power [82–88].

For HRT, there are few data that have investigated sex differences. One study observed a more pronounced HRT response in women. Another study could not see any difference between the HRT values of men and women. However, some studies could show that the HRT response decreases with age [89–91].

There are similarly few and sometimes inconsistent studies on sex-specific differences in BRS. Most, however, found lower BRS values in women [92–95]. But there is also an age dependency for this parameter, BRS decreases with increasing age [94,96].

Electrocardiographic differences between men and women have long been known. The QT interval is a known standard measure of ventricular repolarization. It is heart rate dependent and increases with low heart rate and decreases with high heart rate [97]. Women show significantly longer QT intervals. At an advanced age, sex differences seem to decrease [98,99]. Standard use of Bazett's correction formula may lead to artificial and incorrect QT extension at higher heart rates [100,101]. To avoid this potentially overcorrection, a measurement of the QT/RR relation was developed using regression models [102] and more individual QT/RR patterns [103–108] were found. Numerous studies showed a steeper QT/RR slope in women [100,104,106] indicating a more pronounced extension of the QT interval at low heart rates. There are no sex-specific investigations on post-AMI patients for risk prediction based on QT-interval duration. In epidemiological studies, the general population for both sexes showed an association with total mortality [67,109], cardiac mortality [69], and SCD [70,110] when frequency-corrected QT time was extended.

The QRS vector indicates the main propagation direction of ventricular excitation, while the T-wave vector represents the same for repolarization. Thus, the spatial QRS-T angle characterizes the relationship between depolarization and repolarization waveforms and how homogeneous or heterogeneous the repolarization is [77]. A QRS-T angle measurement close to zero implies that the repolarization direction is approximately opposite to the depolarization direction [97], which should be the case in healthy subjects. An increased QRS-T angle close to 180 degrees again shows maximum orientation differences and the absence of repolarization gradients [97] and this was known to be predisposing to VTs and SCD [76,111]. Some studies on sex differences found that women have smaller QRS-T angles, but it is not sufficiently clear to what extent frequency dependence plays a role here [97,112–114].

In summary, most of the risk predictors listed here are either age-dependent or sex-specific, or both.

Only one study on a postinfarction collective investigated whether a risk prediction separated by sex allows better identification of high-risk patients. On the one hand, they found differences in the predictive power of the individual parameters. For example, different parameters indicate an increased mortality risk in women than in men. While the QRS width is associated with mortality in women but not in men, the mean heart rate is significantly more predictive in men than in women. On the other hand, different, sex-specific optimum dichotomies of the examined parameters were found. An adapted sex-specific model led to a significant improvement in risk prediction in women.

The main limitation of these and all studies for prediction of outcome of patients who survived myocardial infarction separated by sex is the higher prevalence of male patients. Since the proportion of women in postinfarction studies is only 15%–25%, the statistical significance does not usually have sufficient power to allow generally valid statements.

Conclusion

Despite improvements in the treatment of AMI and greater awareness of women's diverging symptoms, more women than men (26% of women and 19% of men) will die within the first-year postmyocardial infarction, regardless of age (3). There are more questions than answers about the underlying cause for the increased mortality in women. When focusing only on malignant arrhythmias and SCD, these events are significantly less common in women. Therefore, they benefit less from ICD implantation than male patients. However, women are more likely than men to develop heart failure independently of LVEF, and appear to benefit more from CRT implantation. Until now, the task of risk stratification after a myocardial infarction has been the early detection of patients who benefit from ICD implantation. In the future, risk stratification, especially in women, must find indicators that focus on heart failure and indicate subclinical decompensation at an early stage to improve outcome.

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Chapter 53

Sex differences in intensive care unit electrocardiographic alarms

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Multiparameter physiologic monitoring, including electrocardiographic (ECG) monitoring, in the intensive care unit (ICU) remains unsatisfactory as evidenced by the well-known alarm fatigue problem. For example, in one study, a single ICU patient generated over 700 alarms per day [1]. At our institution, an average of 187 audible alarms were generated in our ICU per bed per day during a 1-month assessment [2]. Of note, 88.8% of the audible ECG arrhythmia alarms were determined to be false [2,3]. Alarm fatigue occurs when clinicians, mainly nurses since they are typically responsible for bedside ECG monitoring, are desensitized by frequent alarms, most of which are false or do not require a clinical action (i.e., "nuisance" alarms). In 2010, excessive alarm burden was identified as a significant patient safety concern in the public arena, following the death of a patient who was being monitored at a prestigious medical center [4]. Despite multiple heart rate alarms for bradycardia that occurred prior to the patient's cardiac arrest, no one working on the unit that day recalled hearing the alarms. In the investigation that followed, the Centers for Medicare and Medicaid Services reported: "Nurses not recalling hearing low heart rate alarms and finding that some alarms had been adjusted (i.e, turned off or volume lowered), was indicative of ***alarm fatigue,*** and contributed to the patient's death." [4] The most recent data from the past 5 years show that alarm fatigue was responsible for over 650 hospital deaths [5,6], a number believed to be a substantial underrepresentation because of non- or under-reporting. Over time, clinicians/nurses learn to deal with alarm fatigue by: (1) assimilating alarm noise into their workflow, which can lead to an alarm(s) being unintentionally missed; (2) silencing alarms without assessing the patient; (3) lowering the alarm volume; (4) permanently disabling alarms; and/or (5) delaying a response to an alarm [7–13]. These actions place patients at risk for serious adverse events, including death, because true alarms are missed. While clinicians/nurses experience alarm fatigue from repeated exposure to alarms, patients are subjected to both psychological (i.e., fear, sleep deprivation, delirium) [14,15] and physiological (i.e., increased heart rate, blood pressure) stresses from alarm noise [15]. Patients also report being frightened by frequent alarms that often go unanswered [16].

A number of federal agencies and national organizations have issued alerts about alarm safety and alarm fatigue. Since 2007, the Emergency Care Research Institute has placed alarm fatigue at or near the top of its top 10 list of patient safety hazards [17]. In 2014, The Joint Commission established National Patient Safety Goal 6 (NPSG.06), entitled Reduce Harm Associated with Clinical Alarms. Compliance with NPSG.06 requires hospitals to have alarm management strategies in place [18]. The American Nurses Association and the American Association of Critical Care Nurses have issued practice alerts regarding alarm fatigue, emphasizing the need for evidence-based approaches to solve this complex problem [19,20]. While a strong desire to solve alarm fatigue exists from these mandates, over a decade has passed with no substantive progress toward a general solution [21].

False ECG arrhythmia alarms are a major source of alarm fatigue. In a comprehensive evaluation, the frequency, types, and accuracy of physiologic monitor alarms (i.e., ECG, respiration, invasive pressures [arterial, pulmonary artery, central venous, intracranial], and peripheral oxygen saturation or SpO_2) were examined in 461 consecutive ICU patients during a 1-month period [2]. A total of 2,558,760 unique alarms (both audible and inaudible) occurred in the 31-day study period: 1,154,201

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(45%) were arrhythmia alarms; 612,927 (24%) were parameter alarms (i.e., too high, too low); and 791,632 (31%) were technical alarms (i.e., ECG leads off, artifact, line/probe disconnect). Of the over 2.5 million alarms, 381,560 were audible, which equates to an audible alarm burden of 187/bed/day. A total of 12,671 audible ECG arrhythmia alarms were annotated, and 88.8% were determined to be false positive. This study that included consecutive ICU patients represents the largest ECG annotation effort to date and clearly illustrates the magnitude of the alarm fatigue problem.

The number of clinical alarm signals is ever increasing as medical technologies are constantly being added to the ICU environment [22]. Thus, alarm fatigue represents a significant challenge for nurses and other clinicians responsible for responding to alarms and will continue to be a problem in the future as new technologies are introduced into this environment. While many technologies are a potential source of alarm fatigue in the ICU (i.e., ventilators, intravenous pumps, temperature devices, circulatory devices, bed alarms, nurse call lights, etc.), this chapter will focus specifically on ECG monitoring alarms in the ICU setting. The discussion will concentrate in three areas: (1) occurrence rates, accuracy, and types of ECG alarms; (2) causes of false ECG alarms; and (3) interventions tested to date. Each section will provide an overall discussion on the topic and then explore whether sex differences were examined, and if so, if sex differences exist. To reflect current ECG monitoring technologies available in the ICU, only studies conducted in the past 10 years were evaluated for this review.

Occurrence rates, accuracy, and types of electrocardiographic alarms

Two primary approaches have been used to examine occurrence rates, relevance and accuracy of ICU ECG arrhythmia alarms: (1) the total number of ECG alarms, with human annotation to determine true versus false alarms; and (2) the number of actionable versus nonactionable alarms. The definition used to determine "nonactionable" varied across studied, but in general, this term meant the ECG alarm was either false or was valid but did not require a clinical action. Table 53.1 shows studies that have examined the number and type of ECG arrhythmia alarms in the ICU setting separated by ICU type (i.e., adult vs. neonatal/pediatric). As shown, an equivalent number of studies have been conducted in pediatric/neonatal [7,12,13,23,24] and adult ICUs [2,3,10,11,25]. Multiple types of physiologic alarms were typically examined in each study (i.e., vital sign parameter, ECG, oxygen saturation, end title CO_2, waveform data). In the one study that included all consecutive adult ICU patients, of the over 2.5 million alarms (both audible and inaudible), 41% were for arrhythmias (i.e., premature ventricular complexes (PVCs), lethal and nonlethal arrhythmias). The occurrence rate of ECG alarms was lower in all of the other studies, ranging from 0.4 bradycardia alarms per patient per hour [24] to 37% [12] among the pediatric studies, and 1.8%–23% in the other adult ICU studies [10,11,25]. The wide variations in occurrence rates are explained by the types of arrhythmia alarms captured (i.e., only red/crisis level vs. all ECG alarms), the method of data collection (i.e., visual, video, all alarms captured using sophisticated research infrastructure), and the length of the data collection period, which ranged from a few hours to days.

Accuracy of ECG alarms

Consistent in all of the studies was that the vast majority of ECG arrhythmia alarms were false or nonactionable. Nearly 90% of the arrhythmia alarms in the study that used human annotation were false [2,3], and 0%–95% of ECG alarms were false in studies using visual, video, or both methods to determine whether an alarm was actionable [7,10–13,23–25]. In the Rosman et al., study done in the pediatric ICU over a 28-day period, arrhythmia alarms were reviewed from the prior 24 h to determine if relevant ECG alarms had gone undetected, presumably due to alarm fatigue. They identified 1786 ventricular tachycardia (VT) alarms, of which 1769 (99%) were false, mostly due to motion artifact. Of the 17 true VT alarms among five pediatric patients, none were detected by the clinical staff at the time of the event. Importantly, medical treatment in two of the five patients was significantly altered because the VT event was discovered using the daily ECG review process. This study highlights how true alarms, which are infrequent, can become concealed by numerous false alarms, and therefore, are easily missed. Our group found that among adult ICU patients with one or more alarms, only a small number have true ECG alarms (3%), most have false ECG alarms (36%), and 15% have both true and false alarms [26]. This illustrates the significant challenges clinicians/nurses face and how patients can be negatively impacted by alarm fatigue.

Only one study examined whether there were sex differences with regard to true/false alarms [3]. Among 461 ICU patients with 12,671 audible ECG alarms, 11,345 (89.5%) were false. Of the 461 ICU patients, 238 (52%) had one or more false arrhythmia alarms, 12 (2%) had only true arrhythmia alarms, and 211 (46%) patients had no arrhythmia alarms. As shown in Table 53.1, the proportion of females in each group was not statistically different; 49% > 1 false arrhythmia alarm, 42% only true arrhythmia alarms, and 43% no arrhythmia alarms (P-value = .45). There were no sex differences within the

TABLE 53.1 Studies that have examined intensive care unit electrocardiographic (ECG) alarms by the total number of ECG alarms, whether differences were examined by sex, and whether the arrhythmia alarm was actionable or annotated as true.

Intensive care unit type—neonatal or pediatric				
Talley et al. [13]	Pediatric n = 98 (45 days) Data collected by direct observation, interview bedside nurse, or electronic health record	Total # of alarms 2245 from bedside monitor device (i.e., vital signs, ECG, and waveform data). During 45 observational days, there were 2245 alarms, 1 (1.5%) clinically significant arrhythmia. Arrhythmia type not identified. Collected only "three" star alarm data; thus, lower level alarms not captured.	Not reported	Examine actionable alarms Of 2245 alarms recorded, 1 (1.5%) clinically significant arrhythmia occurred during sectioning
Rosman et al. [12]	Pediatric; n = 86 (343 patient days) noncardiac diagnosis Prospective observational data collection of ECG alarms from past 24 h	Total # of alarms 54,656 from bedside monitor device (i.e., vital sign parameter, ECG, oxygen saturation). Of 54,656 alarms, 19,970 (37%) were ECG rhythm alarms, of which 4032 (20%) were "critical" alarm (i.e., asystole, ventricular tachycardia, extreme tachycardia, or bradycardia) and 15,938 (29%) were noncritical ECG alarms (i.e., nonsustained ventricular tachycardia, premature ventricular complexes, pause, atrial fibrillation, high heart rate but less than extreme preset).	Not reported	Examine subgroup of alarms for actionable alarms 3156 (78%) of 4032 critical alarms reviewed, 2273 (72%) false 12,615 (79%) of 15,938 noncritical alarms reviewed, 6376 (50%) false Only VT alarms—of 1786 alarms 1769 (99%) false due to motion artifact
Bonafide et al. [7]	Pediatric ICU and Medical Unit Used video recordings—20 sessions ICU; 20 sessions Medical Unit	Total # of alarms from bedside monitor device 1014 (i.e., vital sign parameter, ECG, oxygen saturation, respiratory rate, end-tidal CO_2). Of the 1,014, a total of 72 (7%) alarms were for arrhythmias. Critical arrhythmia = 1 alarm. Noncritical arrhythmia = 71 alarms.	Not reported	Examine actionable alarms Actionable definition: (1) lead to a clinical intervention; (2) lead to consultation with another clinician; or (3) should have led to intervention or consultation, but alarm unwitnessed or misinterpreted by the staff Critical alarm—of 1 alarm none actionable Noncritical alarm—of 71 none actionable
Van Pul et al. [23]	Neonatal; n = 367 over 1-year period Retrospective review of alarms	Total # of red level alarms from bedside monitor device = 222,751 during 1-year (25 alarms/hour); no total number of ECG alarms provided. 0.4 bradycardia alarms per patient per hour.	Not reported	No examination of actionable/relevant; true/false
Schondelmeyer et al. [24]	5 Children's Hospitals—medical/Surgical unit, Neonatal and Pediatric ICUs Data collected for one 24 h period	Total # of audible alarms 147,213 (i.e., apnea, arrhythmia, O_2 saturation, vital signs exhaled CO_2) during one 24-h period; used census to	Not reported	No examination of actionable/relevant; true/false Of the five hospitals, arrhythmia alarms were first and second most common in

Continued

TABLE 53.1 Studies that have examined intensive care unit electrocardiographic (ECG) alarms by the total number of ECG alarms, whether differences were examined by sex, and whether the arrhythmia alarm was actionable or annotated as true.—cont'd

Intensive care unit type—neonatal or pediatric				
	Used alarm to collect software from monitors and/or central station	calculate the number of alarms per patient day and the number of monitored patients to calculate the number of alarms per monitored-patient day, including only monitored patients in the denominator on each unit at 3 time points, 8 h apart. Total arrhythmia alarms not reported.		two of the pediatric ICU's examined
Intensive ccare unit type—adult				
Gorges et al. [10]	Adult; n = 22 (200 h) Investigator selected one room (randomly) each day (7 a.m.–7 p.m.) and observed alarm responses by clinical team	Total # of alarms 1214 (i.e., ventilator, vital sign parameter, oxygen saturation, feeding pump, IV pump). Of 1214, 134 (11%) were heart rate or arrhythmias (combined).	Not reported	Examine relevant, ineffective and ignored alarms Of 134 heart rate/arrhythmia alarms, 91% ignored/ineffective
Siebig et la. [25]	Adult; n = 68 (982 h) Video and alarm data from bedside monitors collected	Total # of alarms 5820 from bedside monitor device (i.e., vital sign parameter, oxygen saturation, respiratory rate). Of 5820 alarms, 108 (1.8%) were arrhythmia, arrhythmia type not reported.	Not reported	13 of 108 (12%) considered relevant (i.e., followed by diagnostic or therapeutic decision)
Inokuchi et al. [11]	Adult; n = 18 (2697 person-monitored hours) Video and alarm data from bedside monitors collected	Total # of alarms 11,591 from bedside monitor device (i.e., vital sign parameter, ECG, oxygen saturation, respiratory rate, end-tidal CO_2). Of 11,591 total alarms, 2654 (23%) were ECG alarms. Arrhythmia type not identified.	Not reported	Examine relevant alarms Of 2654 ECG alarms, 140 (5.3%) were considered relevant (i.e., immediate clinical examination plus diagnostic or therapeutic decision necessary)
Drew et al. [2]	Adult; cardiac, medical/surgical/neurological; n = 461 31 day study period; consecutive ICU patients; hardware and software system captured every alarm from the bedside monitor—analyzed retrospectively	Total # of alarms 2,558,760 (audible and inaudible) during 1 month bedside monitor (i.e., vital sign parameter, ECG, oxygen saturation); 1,051,054 (41%) arrhythmia. Annotation of the 12,671 audible ECG alarms: Asystole = 792 (6.2%) V-fib = 158 (1.2%) V-tach = 3861 (31%) AVR = 4361 (35%) Pause = 2239 (18%) V-brady = 1260 (9.9%) * 15 alarms (0.1%) were indistinguishable; 1 asystole, 7 VT, 2 accelerated ventricular, 4 pause, and 1 ventricular bradycardia.	Not reported	No examination of actionable/relevant Annotated for # of true/false True alarms Asystole 260/792 (33) Ventricular fibrillation 107/158 (68%) VT 502/3861 (20%) AVR 224/4361 (5%) Pause 272/2239 (12%) V-brady 40/1260 (3%) Total # of false 88.8%
Harris et al. [3] Secondary	Adult; cardiac, medical/surgical/neurological; n = 461 31 day study period;	Total of 461 patients with 12,671 ECG alarms 11,345 (89.5%) false.	211/461 (46%) female	No sex differences among three groups Female/total

Continued

TABLE 53.1 Studies that have examined intensive care unit electrocardiographic (ECG) alarms by the total number of ECG alarms, whether differences were examined by sex, and whether the arrhythmia alarm was actionable or annotated as true.—cont'd

Intensive care unit type—neonatal or pediatric				
analysis of drew et al. [2] study	consecutive ICU patients; hardware and software system captured every alarm from the bedside monitor—analyzed retrospectively	In 461 patients: 238 (52%) patients >1 false arrhythmia alarms. 12 (2%) patients only true arrhythmia alarms. 211 (46%) patients with no arrhythmia alarms.		116/238 (49%) >1 false arrhythmia alarms 5/12 (42%) only true arrhythmia alarms 90/211 (43%) no arrhythmia alarms *P*-value = .45

AVR, accelerated ventricular rhythm; *VT*, ventricular tachycardia; *V-Brady*, ventricular bradycardia.

groups either (i.e., >1 false; only true, no alarms), with nearly equal proportions of female and male ICU patients in each group. This study also showed that sex was not associated with the total number ($P = .126$) or duration ($P = .201$) of false arrhythmia alarms per 24 h of monitoring. Rather, predictors of false alarms included, age >60 years, cardiac or respiratory diagnosis, altered mental status (confusion or agitation), bundle branch block (BBB), ventricular paced rhythms, and or/mechanical ventilation. While the data from the UCSF Alarm Study represent one of the most comprehensive annotation efforts in 461 consecutive ICU patient populations to date, it is not entirely clear whether sex is a factor with regard to ICU alarms [2].

Arrhythmia alarm types

The specific type of ECG arrhythmia alarms was not often reported, rather most studies determined whether the alarm was critical versus noncritical [7,12,13], what the proportion of ECG alarms were when compared with other physiologic alarms [23,24], or if the ECG alarms were actionable/relevant [7,10–12,25]. As mentioned above, Rosman et al. specifically reported on VT alarms (1786 total VT alarms 1769 or 99% false) [12]. Drew et al. reported on audible arrhythmia alarm types. Table 53.2 illustrates the type, number, and rate of false-positive alarms from this study. As shown, accelerated ventricular rhythm was the most frequently occurring audible alarm (34%; with 94.8 false), followed by VT (31%; with 86.8 false). The smallest proportion of audible alarms were for ventricular fibrillation (1.3%; with 32.3% false). The audible alarm burden was 187 alarms/bed/day, which demonstrates not only the auditory burden associated with ECG alarms but also the physical burden since these alarms require clinicians/nurses to silence them.

Causes of false alarms

The specific cause(s) of false ECG alarms was not reported in most of the studies reviewed. One pediatric study described that most false VT alarms were due to motion artifact [12]. The effects of signal quality were examined in two of the adult studies, which reported that three-quarters of ECG arrhythmia alarms were rated as having "good" signal quality at the time the alarm was triggered [2,3]. Good signal quality was defined as a clearly visible P-QRS-T waveform across all seven ECG leads with little noise, baseline wander, or leads off. Only 8.5% of the ECG alarms had poor signal quality (i.e., unanalyzable because of excessive noise, baseline wander, or leads off). While false alarms had a higher proportion of poor signal quality (9.3%) compared to true alarms (0.9%), these data indicate that poor signal quality is not the major source of excessive arrhythmia alarms. We are unaware of any studies that have examined whether the cause of false alarms differs by sex.

Despite no data on sex differences, our group has published several papers identifying several causes of false ECG arrhythmia alarms in adult ICU patients [2,3,27]. Table 53.3 lists conditions identified as sources of excessive false ECG arrhythmia alarms. As shown, persistent atrial fibrillation is one source of excessive ECG alarms. While the goal of an alarm for atrial fibrillation should be to identify both new onset and end-of atrial fibrillation, many current algorithms do not provide these features. This means that atrial fibrillation alarms are especially problematic among ICU patients with chronic atrial fibrillation. Fig. 53.1 shows an ECG from the bedside monitor in a patient with chronic atrial fibrillation who had 1564 individual alarms for atrial fibrillation during a 48 h monitoring period (i.e., 34 alarms/h) [2]. We identified one cause of the repeated atrial fibrillation alarms was due to frequent PVCs or aberrantly conducted impulses (i.e., Ashman's

TABLE 53.2 Illustrates the number, type, and accuracy of 12,671 audible electrocardiographic alarms among 461 consecutive adult intensive care unit patients during a 1-month time period.

Alarm type and algorithm definition	Number of alarms	Number of patients	Number of true positives	Number of false positives	Rate of false positive
Asystole Heart rate drops to 0. No QRS detected for ~5–6 s	792	113	260	531	67%
Ventricular fibrillation Coarse flutter waves without QRS complexes	158	19	107	51	23.3%
Ventricular tachycardia ≥6 consecutive PVCs with rate ≥100 bpm	3,861	183	502	3,352	86.8%
Accelerated ventricular rhythm ≥6 ventricular beats with HR 50–100 bpm	4,361	99	224	4,135	94.8%
Pause 3-second interval without a QRS complex	2,239	140	272	1,963	87.7%
Ventricular bradycardia—≥3 consecutive ventricular beats with HR ≤ 50 bpm	1,260	39	40	1,219	96.7%
Total	12,671[a]	Patient could have had more than one alarm type	1,405	11,251	88.8%

Sex differences not reported
[a]*15 alarms were indistinguishable: 1 asystole, 7 ventricular tachycardia, 2 accelerated ventricular rhythm, 4 pause, 1 ventricular bradycardia.*
From Drew BJ, Harris P, Zegre-Hemsey JK, Mammone T, Schindler D et al. (2014) Insights into the Problem of Alarm Fatigue with Physiologic Monitor Devices: A Comprehensive Observational Study of Consecutive Intensive Care Unit Patients. PLoS ONE 9(10): e110274. https://doi.org/10.1371/journal.pone.0110274.

TABLE 53.3 Conditions identified as sources of excessive false electrocardiographic (ECG) arrhythmia alarms using data from the UCSF Alarm study that included 461 consecutive adult ICU patients with 12,671 audible ECG alarms [2,3,27,34].

Condition identified as a source of excessive ECG arrhythmia alarms
Persistent atrial fibrillation
Artifact mimicking VT or V-fib
Low amplitude QRS complexes leading to false alarms for asystole, bradycardia, and/or pause
Wide QRS due to BBB or ventricular pacemaker rhythm triggering false ventricular arrhythmia alarms
Nonactionable VT and accelerated ventricular rhythm alarms
Electrode failure leading to poor signal quality

phenomenon) during chronic atrial fibrillation. The algorithm in the bedside monitor was designed to generate a new atrial fibrillation alarm following a new arrhythmia, in this case a PVC, leading to incessant alarms, one for atrial fibrillation and one for the PVC. Because many hospitals set atrial fibrillation alarms to an audible setting, incessant alarms will occur until a clinician/nurse turns the atrial fibrillation alarm off, or adjusts the alarm to an inaudible setting. Newer algorithms for atrial fibrillation are being introduced into ICU monitors with a delay feature that will alarm in patients with persistent atrial fibrillation only after a preset time frame has passed (i.e., minutes to hours after

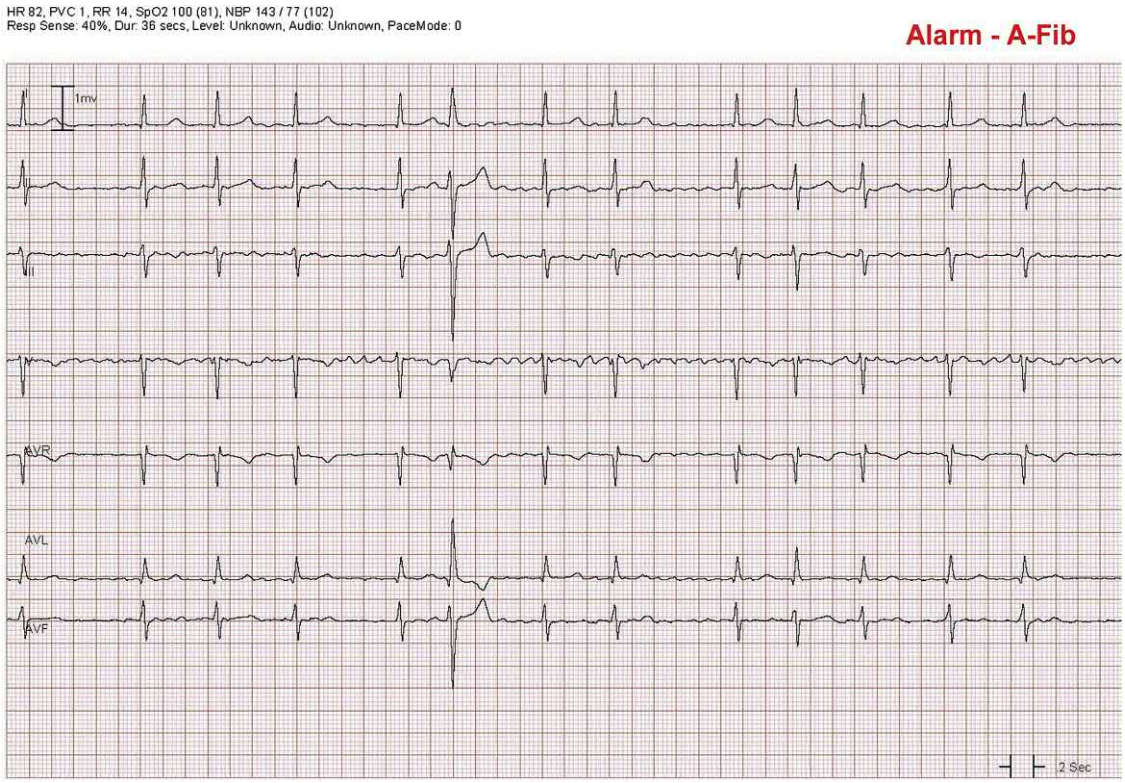

FIGURE 53.1 Seven lead electrocardiogram from the bedside electrocardiographic monitor in an intensive care unit (ICU) patient with chronic atrial fibrillation. This patients had 1564 alarms for atrial fibrillation and 1589 alarms for premature ventricular complexes (PVCs) during a 48 h monitoring period (i.e., ~34 alarms/h). The cause of the repeated new alarms for atrial fibrillation was due to frequent PVCs (sixth beat), that interrupted the atrial fibrillation. The software algorithm was designed to alarm for each new arrhythmia; hence, following every PVC (new arrhythmia), a new alarm for atrial fibrillation occurred.

an alarm). Some newer algorithms are also designed to alarm for the end of atrial fibrillation. Both alarm features are important for clinical management.

Artifact mimicking ventricular fibrillation or VT can also lead to excessive ECG alarms. Fig. 53.2 illustrates an example of a false VT alarm [28]. We have found that it is not uncommon for false ventricular rhythms to have artifact contaminating one or more ECG lead(s), while the other ECG leads clearly show a normal underlying rhythm. Hence, it is very important that multiple ECG leads are displayed for clinicians/nurses to avoid misinterpreting false ventricular rhythms. In addition, manufacturers should design algorithm that use all available ECG leads. Several studies have also examined coupling physiologic waveforms (i.e., SpO_2, arterial blood pressure) with the ECG to reduce false alarms and have had some success with little to no effect on suppressing true arrhythmia events [29–33]. However, one study found that their suppression algorithm did miss true VT (17.73%) and asystole (2.33%) in some instances [30].

A common cause of false alarms occurs in patients with ventricular paced rhythms. In this type of patient, the clinician/nurse is required to activate the "Pace Mode" feature on the bedside monitor, which changes the frequency the algorithm uses to detect pacemaker stimuli, or pacer "spikes." Fig. 53.3 is an alarm for accelerated ventricular rhythm from the bedside monitor in a patient with a ventricular pacemaker. As seen in this example, false alarms for accelerated ventricular rhythm could have been eliminated had the Pacer Mode feature been activated. In the UCSF Alarm study, only 33.3% of patients with ventricular pacemakers had Pacer Mode activated [2]. One could also argue whether accelerated ventricular rhythm should be set to an inaudible setting since this rhythm is seldom treated. Importantly, this particular arrhythmia is one of the most frequently occurring false alarms (Table 53.2). In a recently published paper, we found that none of the 223 true accelerated ventricular rhythm alarms that occurred in 23 ICU patients led to a clinical action (i.e., new/adjustment of medication) or an untoward patient outcome (i.e., code blue, death) [34]. This raises the question about whether accelerated ventricular rhythm alarms should be audible, or even turned on, particularly given the high rate of false alarms generated by this arrhythmia.

Patients with persistent or intermittent right or left BBB generate a high number of false alarms for VT, and/or

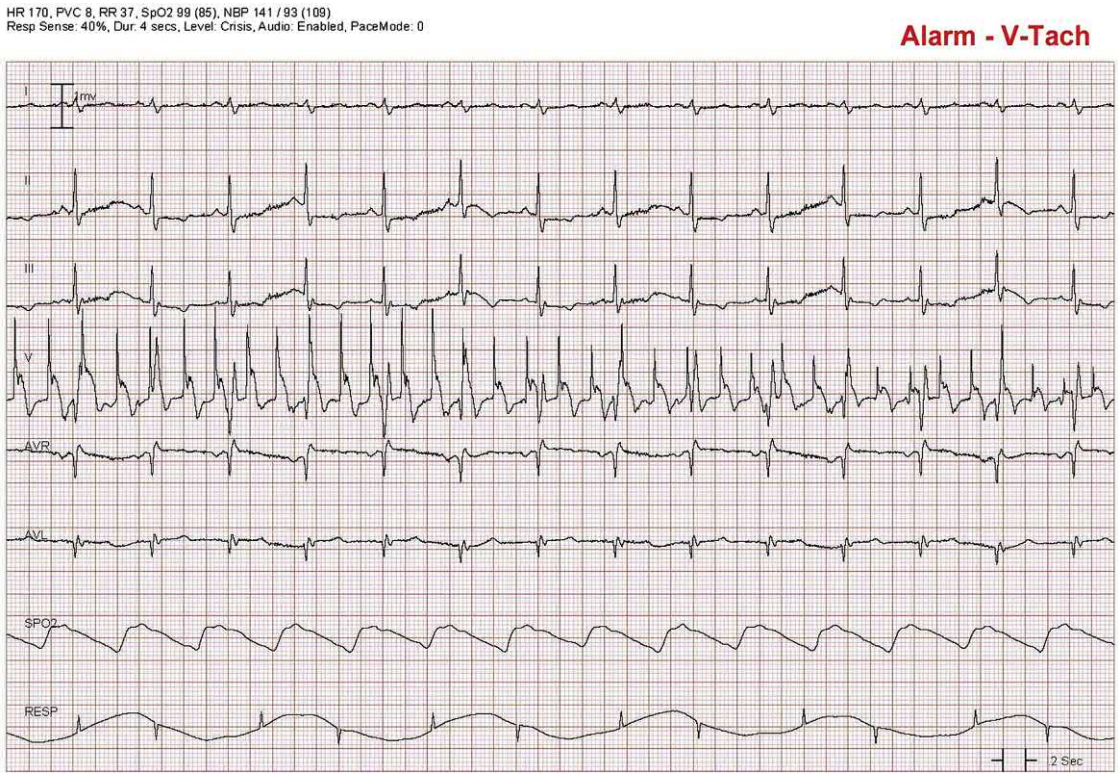

FIGURE 53.2 False-positive ventricular tachycardia (V-Tach) alarm. Note that the ECG waveform in the V lead, which is V1 in our hospital, has the appearance of ventricular tachycardia. However, the other five available ECG leads (I, II, III, aVR, and aVF) show sinus rhythm at a rate of 88 beats per minute, best seen in lead II. Additional proof that this is a false ventricular tachycardia alarm is that the SpO_2 waveform matches the normal sinus rhythm rate. The heart rate (upper left coroner) is 170, which appears to match the spikes in lead V1; hence the QRS complexes in the other leads were not used to determine heart rate. *From Pelter MM, Kozik TM, Al-Zaiti SS, Carey MG. Validation of Displayed Electrocardiographic Rhythms at the Central Monitoring Station. Am J Crit Care. 2018;27(4):339–40.*

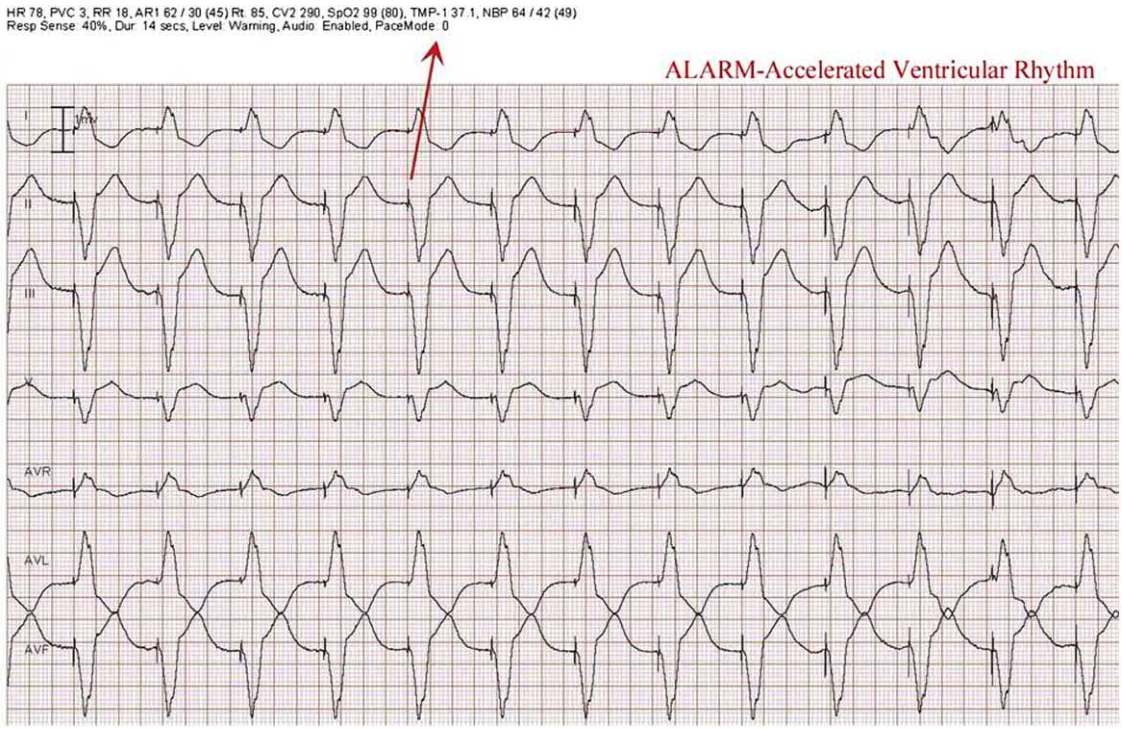

FIGURE 53.3 False electrocardiographic alarm for accelerated ventricular rhythm in a patient with a ventricular paced rhythm. Note the pacer spikes before each QRS complex. However, the Pacer Mode feature was not on (*arrow*), which lead to nonstop false alarms for accelerated ventricular rhythm.

accelerated ventricular rhythm. This problem occurs because the wide QRS complexes associated with BBB are mistakenly identified by the algorithm as a ventricular rhythm. In a multivariate analysis, we found that patients with right or left BBB were 2.2 times more likely to generate false alarms when compared to patients without this ECG feature ($P = .020$) [3]. Current bedside monitor algorithms lack the ability to automatically recognize right or left BBB. However, this ECG feature, which is present in <10% ICU patients [2], causes a significant number of false alarms.

An ECG feature that can also trigger false alarms is the presence of low amplitude QRS complexes [2,3,27]. This type of QRS complex feature can occur in morbidly obese patients, pericardial effusion, and/or BBB. Fig. 53.4 illustrates a 46-year-old female patient admitted to the ICU who had low amplitude QRS complexes. The American National Standard (ANS) for cardiac monitors, heart rate meters and alarms, states that ECG devices should not detect a QRS if the waveform is less than 0.15 mV (1.5 mm) in size [35]. This standard was designed to prevent misdiagnosing P waves as QRS complexes during ventricular standstill. However, some monitor manufacturers elect to use higher QRS detection thresholds (e.g., 0.5 mV or 5 mm) and may require that this higher threshold be present in more than one ECG lead. These more conservative thresholds result in undercounting the heart rate and cause false alarms. In a group of 82 ICU patients with one or more asystole alarms, we found that 45 (55%) had low amplitude QRS complexes (i.e., unidirectional [positive or negative] QRS, >5 mm in two of the four leads used for bedside monitoring [I, II, III, and V1]) on their admitting standard 12-lead ECG. There were no differences in the presence/absence of low amplitude QRS complexes by sex (females—54% no vs. 42% yes; $P = .286$). There was a trend for patients with low amplitude QRSs to have both true and false asystole alarms, but the difference was not statistically significant (5% no low amplitude vs. 13% yes; $P = .229$). In the vast majority of the patients, the asystole alarms were false (95% false no low amplitude QRSs vs. 87% false with low amplitude QRSs; $P = .229$). In the UCSF Alarm study, we found that a sizable QRS complex was readily visible in one or more of the ECG leads in 91% of false asystole alarms, which suggests the algorithm's QRS detection threshold is too conservative and leads to false asystole alarms [2]. Asystole alarms are typically set as crisis level alarms, which means they are "latching" alarms that require a clinician/nurses to

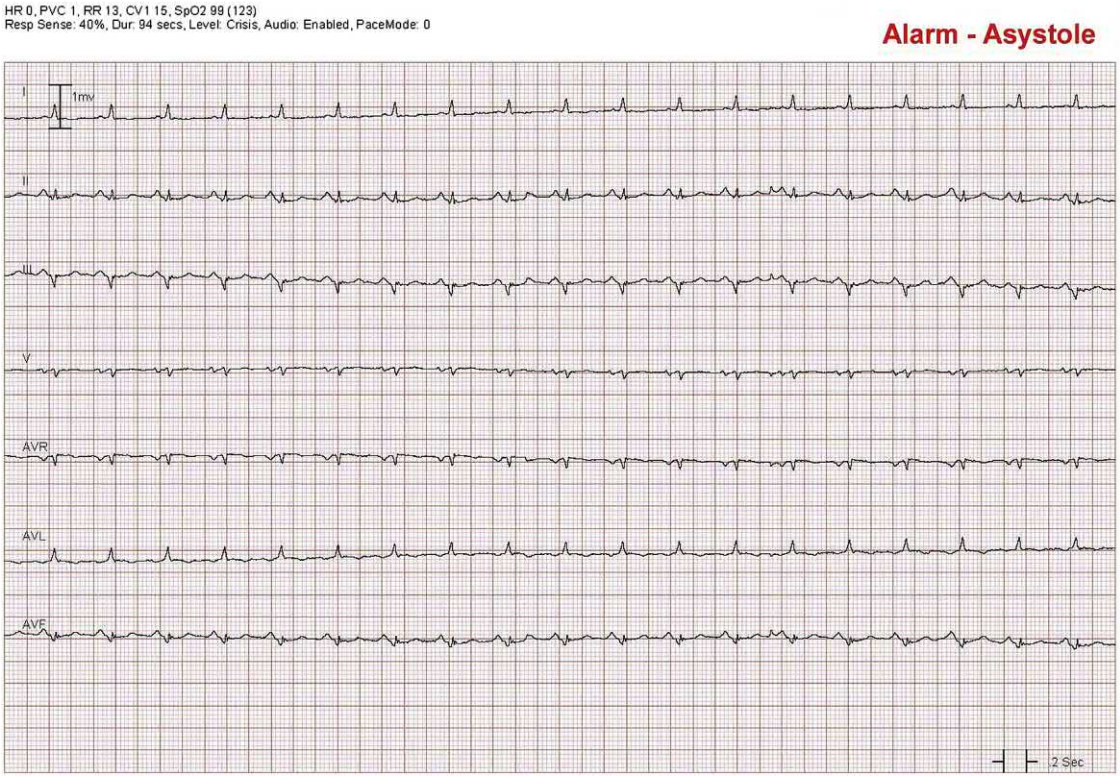

FIGURE 53.4 Illustrates a false asystole alarm in a 46-year-old female admitted to the intensive care unit patient who had low amplitude QRS complexes. The false alarms occurred in this case because the QRS amplitude was less than that required by the algorithm (i.e., unidirectional [positive or negative]) QRS amplitude of 5 mm or greater in two of four leads, which are I, II, III, and V1.

physically push the alarm button to silence them. These alarms are also designed with a high pitch sound to alert clinicians, which can be distressing for patients and families.

Skin electrode failure has been cited as a source of false alarms [36–39]. However, there are scant data on occurrence rates of skin electrode failure from commercially available skin electrodes. There is also no clear guidance on how often skin electrode should be changed to prevent false alarms. Also lacking are studies on the most effective skin preparation protocol that do not cause skin breakdown [2]. Fig. 53.5 is an example of skin electrode failure causing artifact and false VT alarms.

It is important to note that while false ECG arrhythmia alarms are frequent, several studies have reported that the majority of false ECG and other physiological alarms occur in only a few outlier patients. For example, in the UCSF Alarm Study, one patient generated 45% of 12,671 audible ECG alarms [2,3]. This patient had low amplitude QRS complexes in the limb leads, but not in the precordial leads, which was due to left BBB. This phenomenon, labeled "alarm flood," has been reported by others [39–42]. These outlier patients often have ECG features known to cause false alarms including ventricular pacemakers; BBB; and low amplitude QRS complexes [2,3,27]. Two of these studies examined sex as a potential factors and found no differences in the rate of false alarms by sex [3,27]. Importantly, while ECG alarms, which are predominantly false, occur on only a few outlier patients, all patients on a unit are impacted because nursing/clinical care is diverted from others in critical need. Therefore, alarm reduction strategies will not only benefit those at risk for true arrhythmias requiring new/change in therapy but also improve care for all ICU patients because clinicians/nurses would not be constantly assessing false alarms.

Interventions

Prior studies designed to reduce false alarms have included daily ECG skin electrode changes [36–39]; customizing alarm parameters and/or alarm settings [39,42–46]; disposable versus nondisposable ECG lead wires [36,39]; educational initiatives [39,42,43]; and a decision support tool for adjusting for the number of PVCs/hour [47]. In the

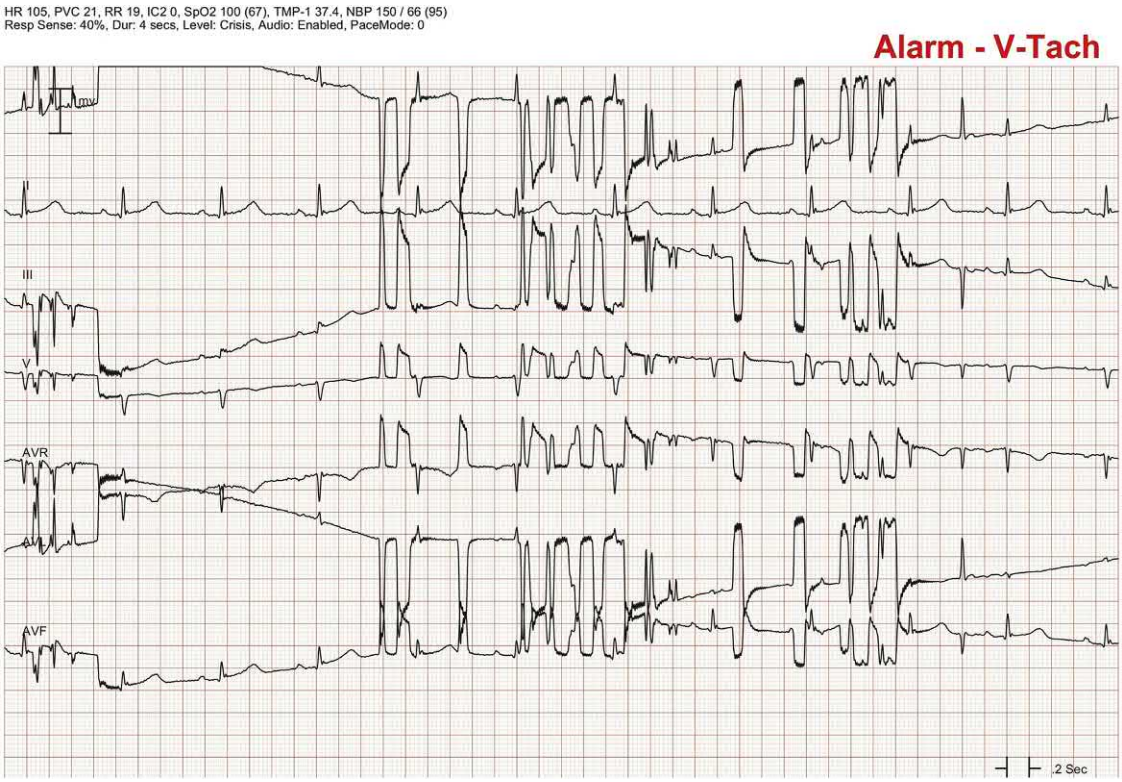

FIGURE 53.5 Electrode failure causing artifact and a false ventricular tachycardia alarm (V-Tach). Electrocardiogram in six of the seven available leads shows intermittent loss of signal (signal "squares off" on top and bottom of tracing) due to an electrode problem such as loss of skin contact or dried out electrode gel. One ECG lead (lead II that uses the right arm and left leg electrodes) does not show electrode failure so the likely electrode that is malfunctioning is the left arm electrode. Failure to apply fresh electrodes in this case will result in numerous false alarms. *Drew BJ, Harris P, Zegre-Hemsey JK, Mammone T, Schindler D, Salas-Boni R et al. Insights into the problem of alarm fatigue with physiologic monitor devices: a comprehensive observational study of consecutive intensive care unit patients. PLoS One. 2014;9(10):e110274.*

study that compared disposable versus reusable ECG lead wires, the investigators reported that the disposable lead wires had fewer technical alarms for lead failure ($P = .03$), but a similar number of alarms for artifact ($P = .44$) [36]. Two studies examined daily electrode changes and showed a reduction in alarms, but no statistical testing was reported [37,38]. However, whether these interventions increased untoward patient events is unknown because only two studies examined adverse outcomes (i.e., missed deterioration, code blue) [38,43]. None of the studies examined whether sex differences were seen.

A number of alarm suppressing ECG algorithms have been examined using a variety of approaches (i.e., relevance vector machine learning, statistical metrics, multilead wavelet signal analysis, time series analysis, spectral regression, various feature discretization, feature selection, and other classifiers) primarily in the laboratory setting [29–31,33,48]. As mentioned previously, several studies have also examined coupling physiologic waveforms (i.e., SpO_2, arterial blood pressure) with the ECG to reduce false alarms and have had some success without suppressing true arrhythmia events [29–33]. However, one study found that their suppression algorithm did miss true VT (17.73%) and asystole (2.33%) in some instances [30].

In one study, a determination of how many true VT alarms were actionable (i.e., 30 s or longer) was examined. This time frame was selected because current guidelines state that VT lasting longer than 30 s should be treated [49]. Of 3861 total VT alarms examined, 502 (13%) were determined to be true positives. Of these, 334 (67%) occurred in one patient with "ventricular storm" whose implantable defibrillator terminated each VT event. Excluding this one patient, there were 168 true-positive VT alarms. Of these, 25 (14.9%) were sustained for 10 s or longer and 12 (7.1%) were sustained for 30 s or longer. All 12 of the alarms that persisted for 30 s or longer were life-threatening events in six patients. Three patients had "do not resuscitate" orders and all three died; the remaining three patients had full resuscitation attempts with two patients dying and one surviving to hospital discharge. These data suggest that VT algorithms designed for identification of sustained VT could improve detection of actionable alarms. Desai et al. examined an algorithm that included whether the VT alarm caused a drop in arterial blood pressure and found this method had a 97% sensitivity and a false positive rate of 45% [31]. Both studies provide useful information about how future VT algorithms might be designed to reduce false VT alarms, which is a major contributor to alarm fatigue. No studies examined whether sex was an influencing factor.

Several studies have examined clinical interventions aimed at reducing false alarms. Most have implemented multiple strategies, or so called "bundles," that include skin electrode protocols, default adjustments to all of the monitors, customization protocols, and staff education and shown some success (30%–50% reduction) without adverse events [21,37,39–41,47,48,50–53]. However, because all of these strategies have been introduced together, it is difficult to identify if one strategy is better than another. In addition, while these studies show some success with reducing the total number of alarms, a substantial number of audible alarms still remain. There is an assumption that a reduction in the total number of alarms and or improving the positive predictive value of alarms will reduce alarm fatigue [21]. However, alarm fatigue is much more complex. One study found that alarm fatigue was multifaceted and was influenced by both working conditions and multiple individual factors possessed by the staff [54]. Studies show that when nurses make monitor adjustments, which is infrequent, for parameter alarms (i.e., heart rate, number of PVC/minute), they make only small incremental changes for fear of missing events and are unsure about how to make monitor adjustments [55–58]. Therefore, much more work needs to be done to address interventions to reduce alarm fatigue while ensuring true events are not missed.

Conclusions

ECG alarms in the ICU setting are frequent, and the vast majority are false. Patient and clinical factors associated with false ECG alarms include age >60 years, altered mental status (confusion or agitation), cardiovascular or respiratory diagnosis, and mechanical ventilation. Sex was not identified as a contributing factor; however, only two studies examine this specifically. Several ECG factors have been identified and include the presence of chronic atrial fibrillation, artifact mimicking ventricular rhythms, low amplitude QRS complexes, wide QRS due to BBB or ventricular pacemaker rhythm, nonactionable VT and accelerated ventricular rhythm, and skin electrode failure. Sex was only examined as an ECG factor in the one study that studied looked at whether low amplitude QRSs contributed to false asystole alarms. No sex differences were found. Interventions tested to date suggest that alarm fatigue is caused by clinicians/nurses and, thus, can be solved by clinicians/nurses (i.e., skin electrode changes, adjusting alarm parameters, and education). However, the primary source of false ECG alarms is rooted in the design of the algorithms built with high sensitivity, to ensure lethal arrhythmias are not missed, but paired with unacceptably low specificity. Hence, interventions tested to date have not addressed the central problem of alarm fatigue, false alarms due to poorly designed ECG algorithms. There is insufficient data to determine if sex differences exist, and if interventions might be more efficacious in men versus women.

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Chapter 54

The predictive value of admission electrocardiography in heart failure

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Introduction

Despite widespread adoption of evidence-based and guideline-directed therapy, hospitalized heart failure (HF) patients continue to experience unacceptably high post-discharge mortality and readmission rates that have remained relatively unchanged for the past two decades [4]. Part of recent effort to improve prediction of cardiac events and mortality in HF patients has been focused on increasing awareness and knowledge of sex differences in cardiac electrophysiology [5]. These differences have been known for many decades. In 1919, Lombard and Cope made the seminal mention of a longer systole in women as compared to men [6], later electrically confirmed as a longer QT interval by 6% or 24 ms [7]. The differences occur in the age ranges of 15−50 years [8]. The clinical significance of this sex difference remained unclear until in the early 1990s when modern medication came into use and Makkar et al. [9] demonstrated that female sex is an independent risk factor for developing drug-induced Torsade de Pointes.

To date, the value of the electrocardiogram (ECG) in predicting cardiac events in men and women has not been conclusively determined. They have not been evaluated in clinical risk stratification tools for HF [10−15]. On ECG, sex differences may be subtle such that on a case-by-case basis, individual differences may overlap sex differences [5]. In addition, individual ECG studies have used ECG data recorded at different times: the first available ECG [12], the latest ECG before death [16], or ECG recorded up to 15 days after admission [17]. These differences affect the relationship between ECG and clinical outcomes since subtle ECG changes may occur when a patient's condition improves, deteriorates, or on medical therapy. The last ECG before death can also identify changes unrelated to a patient's initial presentation such as terminal arrhythmias [17]. This review provides an overview of the current evidence on ECG-based sex differences and the value of admission ECG in predicting cardiac events in men and women with HF.

Sex differences in the electrocardiogram

Patients presenting to the emergency departments with acute HF are at increased risk of morbidity and mortality. Admission ECG is a recommended routine investigation in all HF patients because of its widespread availability, rapidity of results analysis, and usefulness in identifying or excluding potential etiologies [16]. The ECG is also able to detect sex differences in cardiac electrophysiology both in physiological and pathophysiological conditions. The awareness of sex differences in physiological conditions is particularly important to critical care clinicians because they may persist in pathophysiological conditions [5].

Normal individuals

Common sex differences in physiological (healthy) conditions documented in the ECG include basal heart rate, QT interval, QT duration, and QRS voltage [18,19]. Bazett was the first to demonstrate a faster heart rate in healthy women [7]. The Coronary Artery Risk Development in (Young) Adults (CARDIA) study confirmed that women have a higher mean heart rate of 3−5 beats per minute (bpm) [20]. The higher heart rate in women is unrelated to the intrinsic sex-based properties of the sinus node or to differences in autonomic tone [21]. Women also have a longer basal QT interval that persists after correction of heart rate (corrected QT [QTc]). Bazett's formula for QTc revealed 24 ms

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longer QT interval in women compared to men, a finding that was subsequently confirmed in several studies such as (1) in nonhospitalized patients without known cardiac conditions 420 ± 200 versus 400 ± 17 ms [22] and (2) in healthy subjects who had undergone Holter monitoring 457 ± 10 versus 434 ± 12 ms [23]. The prolongation of the QT interval occurred between the end of QRS and the midpoint of the T wave [24].

One proposed mechanism for sex difference in QT interval (or heart rate) is hormonal influence although others such as sex difference in sinus node automaticity and in exercise capacity have been suggested but with inconclusive findings. The evidence for hormonal influence include (1) the absence of sex differences in newborns, children, and older adults (>50 years) [25,26] and (2) the consequence of the shortening of QT interval in men beginning at puberty and lasting until 50 years of age, which corresponds to a period with the highest androgen levels [26]. In addition, ECG pattern of repolarization in castrated men is slower and longer than that of healthy men but normalizes after application of testosterone [27]. In women, differences in autonomic tone and menstrual cycle variability are not responsible for longer QT interval [28].

Other significant ECG-based sex differences in physiological conditions include men having a larger QRS amplitude mostly in leads V3 to V6 [29] possibly due to a larger cardiac mass [19]. On the other hand, women have a significantly shorter QRS and PR duration and smaller precordial lead amplitudes (R, S, T) [30]. Women also have a longer ascending and descending limbs of T wave [31], a shorter PR segment, shorter QRS complex, and narrower QRS voltage [32]. In healthy individuals in exertional activities or athletes in professional sports, men have higher PR intervals (149 ms vs. 141 ms), lead voltage, and QRS duration (98 ms vs. 88 ms) [33]. These differences may have been attributed to small differences in working myocardial cell depolarization and repolarization between men and women [5].

Patients with heart failure

HF is a debilitating progressive condition resulting from pathological changes in either or both cardiac morphology and/or function. These changes can lead to pathological changes in cardiac electrical conduction system captured on ECG as abnormal changes relative to values found in physiological conditions [34]. Similar to physiological conditions, sex differences in ECG have been reported in HF patients. Common sex differences that have been repeatedly mentioned in HF literature include heart rate, QRS width, QRS voltage, QRS duration, T wave, QTc interval, and PR interval [16]. These differences may vary depending on the HF population studied and/or the underlying structural heart disease and may complicate the ability to combine or compare results from individual studies.

In 93 patients with idiopathic right ventricular outflow tract–associated ventricular tachycardia (RVOT-VT), men exhibit a significantly longer QRS duration (99.9 ± 19.4 ms vs. 88.4 ± 20.7 ms, $P = .02$) and RV mean voltage (3.7 ± 0.9 mV vs. 3.0 ± 0.7 mV, $P = .03$) [31]. In a related study enrolling 384 patients with Brugada syndrome, men had a greater ST segment elevation (3.5 ± 1.8 mm vs. 2.5 ± 0.7 mm; $P < .001$) and longer QRS duration (107 ± 17 ms vs. 98 ± 19 ms; $P < .001$). However, the difference in QTc and PR interval between men and women was not significant [36]. In 116 HF patients with documented left ventricular (LV) hypertrophy, and after adjusting for LV mass, height, and weight, men had a significantly longer QRS duration (108 ± 11 vs. 97 ± 11; $P = .0001$), 2-lead sum of voltage (18,764 vs. 17,327), and R-wave amplitude (818 vs. 626; $P = .05$) [37]. Briefly, the reviewed studies demonstrate that in HF, men have a longer QRS duration, QRS amplitude, and ST segment elevation compared to women, while sex difference in QTc interval and PR interval is not significant in HF patients.

Predictive value of admission ECG in HF patients

In all heart failure patients

The 2016 ESC guidelines recognize the importance of ECG in the diagnosis and prognosis of HF patients. The guidelines recommend ECG to all HF patients at presentation to assess potential etiology, inform appropriate therapy, and predict cardiac events [34]. The guidelines also indicate that normal ECG findings are unlikely in HF patients [16]. In support of these recommendations, current data on some ECG parameters including QRS duration, T wave, ST-segment elevation, and/or depression at presentation strongly support their ability in predicting cardiac events and clinical outcomes in HF patients [38–41].

In HF patients, QRS duration is one of the most frequently reported ECG parameters associated with increased likelihood of future cardiac events. Prolonged QRS duration (≥120 ms) is highly prevalent in HF patients ranging from 14% to 47% [38]. It has a significant correlation with worsening LV function (depressed LV ejection fraction) and unfavorable prognosis [38–40]. Prolonged QRS duration (≥120 ms) in patients with Takotsubo cardiomyopathy has a significant independent association with increased 60-month mortality [40] and a threefold increase in the risk of combined endpoint of mortality and/or heart transplantation [41], in-hospital mortality (OR 5.06,

$P = .002$), and cardiac death (OR, 7.34, $P = .02$) [42]. When combined with B-type natriuretic peptide concentration (>400 pg/mL), prolonged QRS duration is a significant univariate and multivariate predictor of all-cause death, cardiac death, and pump failure [43]. In fact, increasing QRS duration—120, 120−160, and >160 ms—strongly correlates with 20%, 36%, and 58% of mortality at 36 months, respectively [40].

Other significant ECG parameters on admission that can predict cardiac events in HF patients include QTc duration, changes in ST segment, low voltage, and Q waves. Admission ECG done on 246 consecutive HF patients demonstrate that QTc peak duration (≤360 ms) is a significant multivariate predictor of a composite endpoint of cardiac events, rehospitalization, or death (OR 2.50, $P = .009$) [44]. The prognostic value of the presence of atrial fibrillation in HF patients has been known for decades; in a cohort of patients admitted with acute HF and were followed for 30 days with regard to cardiac events, those patients with an event had a significantly higher incidence of atrial fibrillation on admission ECG as compared to those without [42].

In HF patients presenting with symptomatic cardiac ischemia, T-wave (OR, 1.68, 95%, CI; 1.36−2.08) and ST-segment elevation (OR 1.62, $P < .001$) are significant multivariate predictors of death and myocardial infarction (MI) [45]. Consistent with these findings, Ma et al. [46] evaluated 203 consecutive patients with acute MI and reported a significant correlation between ST-segment depression in leads aVL, V4−V6, and multivessel cardiac disease. In support, a post-hoc multivariate analysis of the TIMI III Registry ECG Ancillary Study enrolling patients with unstable angina and non−Q-wave MI reported ST-segment deviation of ≥1 mm or ≥0.5 mm is an independent predictor of death or MI within 12 months [47]. In addition to ST segment deviation (elevation or depression) in patients with acute major pulmonary embolism, complete right bundle branch block, peripheral low voltage, and Q waves are significant independent multivariate predictor of 30-day postdischarge mortality [48].

Heart failure by sex

Although sex differences in ECG has been well documented in HF literature, trials on clinical significance of these sex differences have a disproportionate and indiscriminate focus on all HF patients. Only a few trials have specifically examined the relative performance of ECG-based sex differences in predicting cardiac events or mortality in men and women. There is also underrepresentation of women in some of these trials, which limits a holistic understanding of the predictive value of ECG-based sex differences [38]. Moreover, comparative analysis and a uniform understanding of the predictive value of sex differences in ECG in HF patients has been complicated by individual trials examining ECG parameters in HF patient populations diagnosed with different underlying structural heart disease or arrhythmias such as RVOT-VT, Brugada syndrome, MI, and symptomatic cardiac ischemia syndrome. However, the few trials examining ECG-based sex differences in HF population at presentation provide an insight into their value in predicting sex-based cardiac events.

In a post-hoc analysis of Beta-Blocker Evaluation of Survival Trial (BEST) enrolling 2708 patients with New York Heart Association (NYHA) Class III/IV and LVEF ≤ 35%, baseline QRS duration was a significant univariate and multivariate predictor of mortality in men (HR: 1.006, $P = .0001$) but not in women (HR: 1.00, $P = .1642$) [37]. Comparable findings were reported in a follow-up sex-stratified analysis of the 1851 participants from the Strong Heart Study (SHS) [49]. The study compared QRS duration and cardiovascular events in American Indian men versus women. Women in the highest QRS quintile (≥105 ms) compared to those in the lowest quintile (64−84 ms) had an independent and significant increase in the risk of cardiovascular events (HR 1.6, 95% CI 1.1−2.4). When included in the SHS Coronary Heart Disease Risk Calculator for future cardiovascular events, prolonged QRS duration significantly improved prediction of future CHD in women (Net Reclassification Index 0.17, 95% CI 0.06−0.47). This relationship however was absent in men [49]. However, analysis of KF patients with RVOT-VT reported divergent findings. The patients did not exhibit any significant differences in QRS duration and voltage, QTc, and T wave in predicting VT recurrence [35]. Similarly, in patients with Brugada syndrome, QRS duration and ST-segment elevation did not predict cardiac events but predicted positive treatment response to sodium blockers in women [36].

In a subsequent analysis of the Women's Ischemia Syndrome Evaluation (WISE) study, Triola et al. [50] evaluated predictive value of ECG in cardiovascular outcome in 143 women. Significant independent predictors of future cardiac events in women with MI included a wider QRS-T angle (electrical angle between QRS complex and the T wave), wider QRS complex, longer sex and age-adjusted QT interval, and depressed ST segment in precordial leads [50]. Corroborating evidence was reported in a subsequent study by Mieszczanska et al. [51], which evaluated sex-related disparity in ECG parameters and their predictive value in cardiac events in 838 patients with MI. In the study, women had faster heart rate and longer QTc duration, and more lateral ST depression and T-wave inversion in anterior and lateral region but shorter QRS duration compared to males. Multivariate analysis of ST-

segment elevation in anterior leads V1−V4 was associated with increased risk of recurrent events in females (HR 2.16, $P = .003$) but not in males (HR 0.81, $P = .32$). Finally, ST segment depression in lateral leads V5−V6 or AVL predicted recurrent cardiac events in males (HR 1.70, $P = .006$) but not in females (HR 0.98, $P = .93$).

Sex differences in ECG findings prior to sudden cardiac death (SCD), in the use of cardiac resynchronization therapy (CRT) and across race and ethnicity have also been reported. The annual incidence of SCD in women is almost half that of men but with a significantly slower decline. Underlying conditions associated with SCD risk is more difficult to recognize in women. In an autopsy analysis, females are more likely to have normal ECG than men prior to SCD (22% vs. 15%; $P < .001$) more so in female patients with nonischemic causes of SCD (27% vs. 16%; $P = .009$) [3]. However, while CRT with pacemaker or defibrillator is indicated for the prevention of SCD, the use of CRT in women is significantly lower than that in men [52]. Finally, race and ethnicity have been associated with sex differences in ECG in HF patients. Atrial fibrillation and QRS interval >120 ms are more prevalent in white than in black patients, while Hispanics have the highest prevalence of paced rhythm, left bundle branch block, and more frequent abnormal QT intervals than whites and blacks [53].

Implications for prognosis

HF population continues to grow with about 55% being women. However, in many of recent HF trials, women are by far underrepresented [54]. For example, the proportion of women was between 11 and 16% in SOLVD prevention or MADIT-II whereas it was between 30 and 40% in COMPANION or CHARM-preserves, among others [54]. Furthermore, many standardized ECG criteria for HF do not evaluate sex differences resulting in reduced sensitivity and accuracy in risk stratification of women. This is despite widespread availability of ECG as well as leading HF guidelines recommending its use in all HF patients on admission [34,55]. For healthcare providers and cardiologists in particular, it is critical to understand the role of sex differences in the recognition, diagnosis, prognosis, and management of HF. With increasing evidence of sex differences in ECG in both physiological and HF conditions, the utility of ECG in predicting sex-specific cardiac events seems promising.

In summary, significant differences in ECG parameters conducted on admission could have important implications for prognosis and clinical management of HF patients. QRS duration, T angle, QTc interval, and ST-segment deviation in women and QRS duration and ST depression in men can predict cardiac events and mortality. Thus, inclusion of these ECG-based sex differences in current risk stratification tools can lead to more accurate and sex-specific criteria for prognostication of HF. In fact, combining prolonged QRS duration with BNP [43] or its inclusion in the SHS Coronary Heart Disease Risk calculator [49] have been shown to improve the prediction of death and cardiovascular events, respectively.

Despite prognostic significance of ECG-based sex differences, the lack of consistency in their predictive value have been observed in some studies suggesting an effect of the underlying structural heart diseases. For instance, many studies have shown QRS duration and ST-segment deviation to be an independent predictor of cardiac events in both female and male HF patients [37,42,49]. However, in patients with heart-rhythm disturbance disorder such as Brugada syndrome and RVOT-VT, QRS duration, and ST-segment deviation do not predict cardiac events [35,36]. Thus, the effect of structural heart disease on ECG-based sex differences warrants additional clinical trials to clarify the predictive value of ECG on cardiac events in female and male HF patients and possibly define appropriate sex-specific treatment strategies.

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Part XIII

Ventricular tachycardias

Chapter 55

Ventricular arrhythmias associated with structural changes

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Introduction

Ventricular arrhythmias represent a group of clinical conditions with irregular heart beat originated in the ventricles. They cover a wide spectrum of findings, ranging from benign premature ventricular complexes (PVCs) in normal subjects to ventricular tachyarrhythmia, ventricular fibrillation, and torsade de pointes resulting in sudden cardiac death [1]. Although they are less frequent than atrial arrhythmias, they represent serious clinical and public health problems, and one of the leading causes of mortality in the Western countries.

Although ventricular arrhythmias can occur also in patients without structural heart disease [2], they are commonly associated with structural changes of myocardium that create arrhythmogenic substrate. Arrhythmogenic substrate is a term comprising complex changes in myocardium affecting active and passive electrical properties of myocardium and creating conditions for triggering and maintaining arrhythmias.

Clinical and basic science studies have shown essential sex differences in cardiac structure and electrical characteristics that could consequently have an impact on the occurrence of ventricular arrhythmias. These differences have been observed under physiological as well as under pathological conditions. The sex differences in structural remodeling interrelated with electrical remodeling in cardiac pathology can be observed from the organ level to tissue and cellular levels, ion channels and gene expressions, clinically, e.g., in a lower occurrence of structural heart disease as a precursor to sudden cardiac arrest in women [3–5]. This chapter reviews structural changes of myocardium in the most common cardiac pathologies leading to ventricular arrhythmias with the focus on the sex differences from female perspective.

Physiological sex differences

The hearts of women are smaller. It has been documented for both left ventricular (LV) and right ventricular (RV) dimensions, as well as for LV and RV mass. Both absolute values and values of indexed left ventricular mass (LVM), measured with any imaging methods (M mode echocardiography, 2-dimensional echocardiography, 3-dimensional echocardiography, the 64-multidetector row computed tomography, CMR), are consistently smaller [6–9]. Since the dimensions of the right and left ventricles are smaller, consequently the end-diastolic and stroke volumes are smaller [10,11].

On the other hand, the LV and RV ejection fractions are higher. The LV longitudinal and circumferential strain is higher in women, as well as the larger LV twist and a faster untwisting velocity during large reductions to preload compared to men [10].

There are also differences in the myocardial tissue structure. Using cardiac magnetic resonance, sex differences in healthy persons were shown, namely the higher extracellular volume (ECV) in women compared to men, and less ECV changes with aging [12–14].

Women and men differ also in electrophysiological and ECG characteristics. In the postpubertal phase, women have longer action potential (AP) duration [14]. Studies in humans show that women have higher resting heart rate, shorter QRS complex duration, longer QT-interval duration (both uncorrected as well as corrected), and different pattern of ventricular repolarization [15]. Women have lower QRS complex amplitude, and this difference is present also after adjustment for differences in LVM and body weight [16]. Since the QT interval includes the duration of both depolarization (QRS complex) and repolarization (T wave), it means that the main difference in

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the QT interval is due to longer duration of repolarization. Since these differences appear in puberty, it suggests that sexual hormones play a key role [15,17] (Fig. 55.1).

During the fertile period, the sex differences in electrophysiological characteristic can be further modified by menstrual cycle. Although no significant difference was found in the corrected QT interval among the three phases of menstrual cycle, menstrual phase, follicular phase, and luteal phase, the differences appeared after double autonomic blockade (DAB) [17]. The corrected QT interval was shorter in the luteal phase compared to the menstrual or follicular phase. Similarly [18], Endres showed no significant differences among the three phases of menstrual cycle in ST segment height, T-wave amplitude, and QTc interval. But after DAB, differences between follicular and luteal phase appeared, namely significantly higher values of ST segment height, J point/QRS, 40 ms/QRS, and QTc. Differences in these parameters do not appear to be

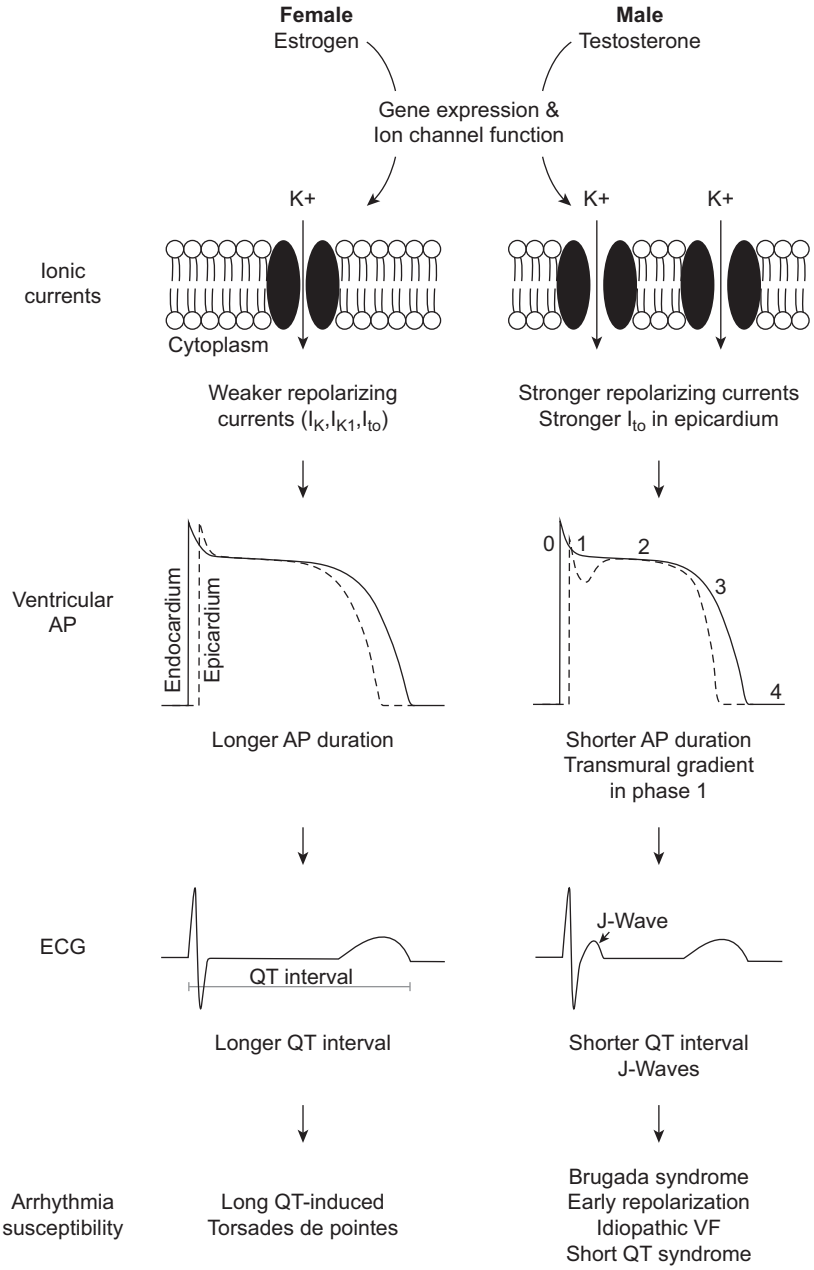

FIGURE 55.1 Sex differences in ventricular cardiomyocyte electrophysiology. *AP*, action potential; *ECG*, electrocardiogram; *IK*, delayed rectifier K^+ current; *IK1*, inward rectifier K^+ current; *Ito*, transient outward K^+ current; *VF*, ventricular fibrillation. *Reprinted from Tadros R, Ton AT, Fiset C, Nattel S. Sex differences in cardiac electrophysiology and clinical arrhythmias: epidemiology, therapeutics, and mechanisms. Can J Cardiol 2014;30(7):783–92. with permission from Elsevier.*

responsible for the sex differences, but they can be manifested after DAB, or in combination with other pathology. In the ovulation period, the heart rate significantly increased as compared to menstruation period, and the J-T peak is shorter [19]. It can be speculated that differences in myocardial repolarization modulated by sex hormones can contribute to the differential presentation of arrhythmias in men and women [20].

Significant prolongation of QTc interval was observed in pregnancy [21]. Women are less prone to arrhythmias during pregnancy [22], but the incidence of arrhythmias can increase in women with preexisting heart disease or who had ventricular tachycardia before pregnancy [3,23,24].

Summarizing, sex-specific differences in anatomy, structure, and electrophysiology modulated by hormonal status are present already under physiological conditions and can interplay with pathological processes.

Ventricular premature complexes

The most common ventricular arrhythmia is ventricular premature complexes—ectopic impulses originating from an area distal to the His–Purkinje system.

PVCs are observed in 1% of clinically healthy people as detected by a standard ECG, and in 40%–75% of apparently healthy persons as detected by 24–48 h ambulatory (Holter) ECG recordings [25,26]. Although they can occur in the absence of identifiable cardiac disease, and thus considered as relatively benign [26,27], they are frequently associated with structural changes of myocardium and can indicate an increased risk of sudden cardiac death [28,29].

The PVCs' prevalence is lower in women compared to men of the same age and the prevalence is also lower in women with coronary heart disease than in men with coronary heart disease [30]. As was shown by Dogan [19], a significant decrease in the number of PVCs in ovulation period as compared to the menstrual period was observed, suggesting a protective effect of estrogen. During pregnancy, the number of ventricular premature beats can increase, but is benign in most patients [31].

The clinical significance of PVCs is related to the frequency and characteristics of PVC, and to the type and severity of associated structural heart disease. The increased risk of death, all-cause mortality, and sudden cardiac death, associated with incidence and complexity of PVCs, has been observed in coronary heart disease [30,32], in MI patients [33–35], coronary artery disease and dilated cardiomyopathy [33,34], hypertension and LV hypertrophy [32,36,37], and obesity [38].

Life-threatening arrhythmias

The prevalence and incidence of the life-threatening ventricular arrhythmias and sudden cardiac death are generally lower in women than in men. Women are less prone to ventricular arrhythmias [22,39]; they have lower incidence of sudden cardiac death—only about 20% of SCD [3,20,23,40]—and lower frequency of spontaneous or inducible ventricular tachycardia [23]. On the other hand, there is higher percentage of women with symptomatic long QT syndrome and occurrence of drug-induced torsade de pointes [23].

Three main mechanisms are involved in pathophysiology of life-threatening ventricular arrhythmias: increased automaticity, reentry, and triggered activity. Reentry is the mechanism underlying most ventricular arrhythmias associated with structural changes, in combination with functional alteration of electrogenesis and electrophysiological heterogeneity. Additional factors involved in women are hormonal status and phases of the women's life.

Women differ in the presence of conditions that can lead to structural changes of ventricular myocardium. Women are less likely to have diagnosis of coronary artery disease, LV systolic dysfunction [5]; they have lower prevalence of left ventricular hypertrophy (LVH) compared to men with comparable blood pressure [41]. Women are more likely to be obese and have higher prevalence of the class 3 obesity [42]. Differences have been reported in visceral obesity [43,44]. Sex differences from women's perspective are summarized in Fig. 55.2.

Coronary artery disease

Coronary artery disease is the most frequent cause of ventricular arrhythmias and sudden cardiac death [1,5]. The substrate for arrhythmia is created by the heterogeneity of the myocardial tissue. Advanced imaging methods allow the assessment of structural changes in coronary artery disease, such as fibrotic scars, edema, microvascular obstructions, diffuse or regional fibrosis, and areas of necrosis with islands of viable cardiomyocytes especially in the periphery of the infarcted area (periinfarct zones), resulting in tissue heterogeneity. These regions create areas of altered activation propagation generating conditions for the development of lethal reentrant arrhythmias [45–51].

Women develop coronary artery disease on average 7–10 years later compared to men [52], showing a "female advantage" in the premenopausal women compared with age-matched men. This "sex protection" decreases after menopause [53].

Sudden cardiac death is less common in women; the lower frequency of SCD in women with CAD is lower also after adjusting for age and this difference is not explained by the risk factor burden [54,55]. Episodes of ventricular arrhythmia and the number of more severe arrhythmias are less frequent in women with CAD treated with an ICD compared to men [56]. On the other hand, women have a higher risk of torsade de pointes due to antiarrhythmic drugs [57].

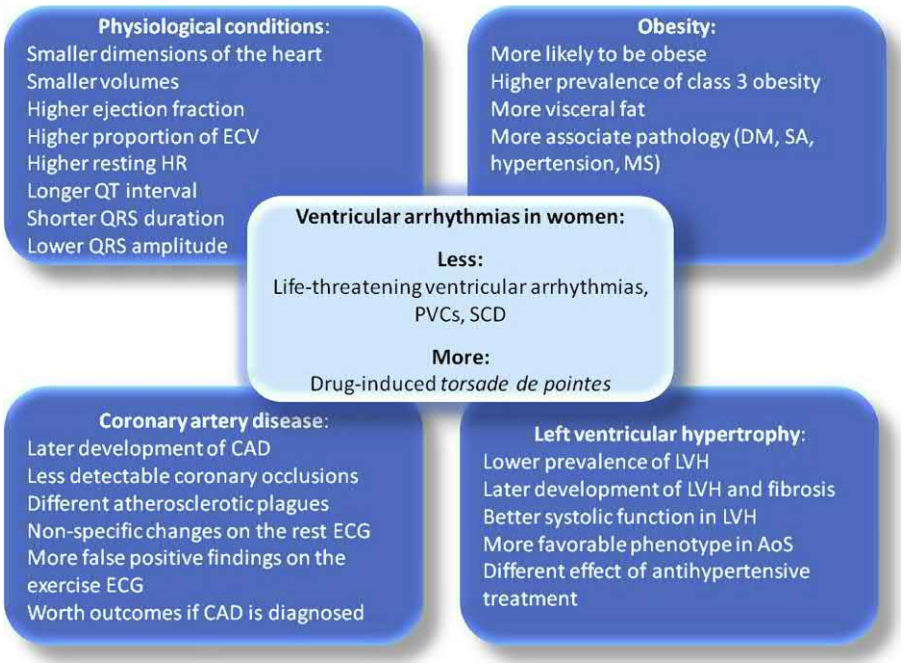

FIGURE 55.2 A scheme summarizing the main sex differences related to structure and ventricular arrhythmias from women's perspective. *CAD*, coronary artery disease; *DM*, diabetes mellitus; *ECV*, extracellular volume; *HR*, heart rate; *LVH*, left ventricular hypertrophy; *MS*, metabolic syndrome; *PVCs*, premature ventricular contractions; *SA*, sleep apnea; *SCD*, sudden cardiac death.

Although ventricular arrhythmias are less frequent in women, still it is a significant clinical and public health problem, and, more importantly, the decline in SCD rates among women has been markedly less than that observed for men [58].

Differences in anatomy

Physiologically, women have smaller coronary arteries, this difference is not related to the body habitus or LVM [59,60]. It is associated with higher coronary flow and higher endothelial shear stress [61]. Autopsy studies showed that women have less extensive atherosclerotic burden compared to men [62–64]. Using quantitative coronary angiography and radiofrequency intravascular ultrasound, the PROSPECT Study analyzed sex differences in patients with acute coronary syndrome with the focus on formation, vulnerability, extent, and composition of coronary plaques. It was found that women have less extensive coronary artery disease with fewer and more focal nonculprit lesions. Nonculprit lesions had significantly less plaque rupture, less necrotic core, and dense calcium, fibrous, and fibrofatty tissue [65].

There findings suggest that the impact of ACS syndrome in men and women may differ. It has been suggested that estrogen might retard plaque development, stabilize existing plaques, and prevent their rupture in women [66].

Taking together, on the one hand, women have a lower prevalence of obstructive CAD by coronary angiography, and more often preserved LV function as compared to men [67,68]; on the other hand, they have a higher prevalence of symptoms, a higher rate of functional disability, and women with ischemic heart disease have more adverse outcomes as compared with men [69–71].

Although standard imaging methods show lower prevalence of obstructive CAD, it has been shown that coronary microvascular dysfunction—a prognostically important finding in patients with symptoms suggestive of coronary artery disease—does not differ between women and men [61,72]. It is possible that the functional alterations are associated with structural changes not detectable with standard imaging methods, such as coronarography or echocardiography. Since these methods are frequently used as reference methods in comparative studies with ECG, a question arises regarding the ECG changes in CAD, as markers of changes in electrophysiology (Fig. 55.3).

Reduced blood supply results in changes in the active and passive electrical properties of the myocardium. At the cellular level, a decreased transmembrane resting potential and changes in AP morphology, as well as slowing in ventricular activation, were documented in the affected area [73–77]. The heterogeneity of electrophysiological properties together with structural changes, such as fibrosis and inflammation, create conditions for ventricular arrhythmias, for triggering impulse generation and initiating and maintaining reentry.

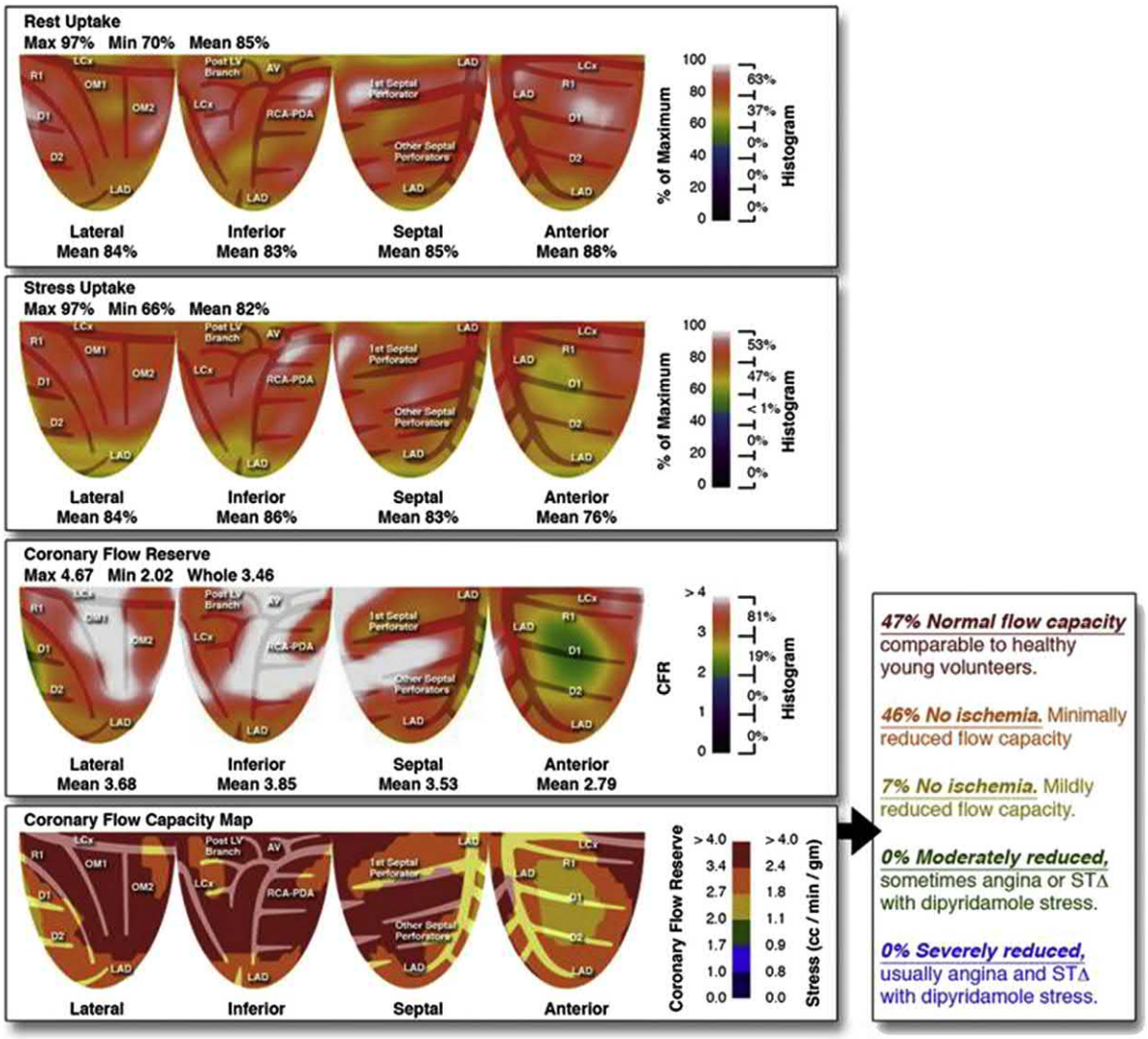

FIGURE 55.3 Myocardial perfusion imaging in women: Overdiagnosis versus microvascular disease. Rest and stress relative uptake images, coronary flow reserve, and coronary flow capacity map combining stress flow (in mL/min/g) and coronary flow reserve. *CFR*, coronary flow reserve; *D1 and D2*, diagonal branches; *LAD*, left anterior descending coronary artery; *LCx*, left circumflex coronary artery; *OM1 and OM2*, obtuse marginal branches; *PDA*, posterior descending artery; *RCA*, right coronary artery; *RI*, ramus intermedius. *Reprinted from Patel MB, Bui LP, Kirkeeide RL, Gould KL. Imaging microvascular dysfunction and mechanisms for female-male differences in CAD. JACC Cardiovasc Imaging 2016;9(4):465–82, with permission from Elsevier.*

The rest ECGs in women with coronary artery disease show nonspecific ECG changes, frequent ST-T changes, and lower QRS voltage [78,79]. Although women are less likely to develop ST segment elevation myocardial infarction (STEMI) [80,81], they have more frequently ST segment changes on the stress ECG. These ST segment changes at the stress ECG are frequently assigned as "false"—"false positive"—since they are not in agreement with results of standard imaging methods used as reference, with, e.g., echocardiography [82]. However, considering the possible effect of coronary microvascular dysfunction, they can be reflections of the underlying processes affecting electrogenesis.

The additional factor contributing to sex differences is the interference with the effect of endogenous estrogen in premenopausal women and hormone replacement therapy in postmenopausal women [83–87].

Summarizing, women have less detectable coronary occlusions, different atherosclerotic plaques, nonspecific changes on the rest ECG, and less ventricular arrhythmia. On the other hand, they have more complains, more false-positive finding on the exercise ECG, and worth outcomes if coronary artery disease is diagnosed. Differences in coronary microvascular dysfunction could contribute to understanding these differences.

Obesity

The high prevalence of obesity and its increasing trends in majority countries represent a serious public health problem [88–91]. Prevalence of premature ventricular contractions in obese patients with eccentric LVH is 30 times higher compared with lean persons [92]. Ectopic ventricular arrhythmias during exercise, defined as multiple ventricular premature beats, ventricular bigeminy, nonsustained ventricular tachycardia, or sustained ventricular tachycardia, are more frequent in obese subjects [93]. Obesity is associated with a higher risk of ventricular arrhythmias and sudden cardiac death [94–96]. Additionally, obesity is frequently associated with metabolic disorders and other comorbidities such as metabolic syndrome, type 2 diabetes, hypertension, and sleep apnea; these conditions further increase the risk of arrhythmias [96] (Fig. 55.4).

Women are more likely to be obese and have higher prevalence of the class 3 obesity [90]; these findings contrast with the lower occurrence of ventricular arrhythmias in women compared to men.

Structural changes in obesity

Obesity is associated with the increase in epicardial and intramyocardial adipose mass and LV hypertrophy. It affects the heart in several ways. The fatty infiltration of myocardium affects cardiomyocytes and interstitium, as well as the metabolism of the heart. The proportion of the active myocytes (the "free-fat mass") and adipose tissue is changed in favor of the adipose tissue [97]. The epicardial and pericardial adipose tissues play role in the secretion of adipokines and chemokines that can stimulate inflammation. It is associated with the production of cytokines and chemokines that can affect electrical functions such as the presence of gap junctions [98]. Additional remote effect has the systemic secretion of adipokines, cytokines, and metabolites [99]. The effect of these factors is multiple, leading to mitochondrial dysfunction, oxidative stress, autophagy, mitophagy, autonomic dysfunction, and cardiomyocyte death. Consequently, electrogenesis is altered and conditions for conduction block and aberrant electrical signals are created.

It is possible that the effect of obesity on LV myocardium in women is related to their body composition, namely to visceral distribution of the fatty tissue [97]. The ratio of fat-free myocardial mass and adipose mass differs between obese women and men. Women have more frequent a relative deficiency of fat-free mass and excess of adipose mass ("sarcopenic obesity") [100,101].

ECG abnormalities in obesity include leftward shifts of the QRS and T-wave axes, low QRS voltage, ECG sign of LVH, T-wave flattening, increased duration of the QRS complex and QT interval, increased QT dispersion, and the presence of late potentials [102–104]. Some of them are recommended as potential markers of sudden cardiac death, especially the increased duration of the QRS complex and QT interval, increased QT dispersion, and the presence of late potentials and fragmented QRS complex [105–107].

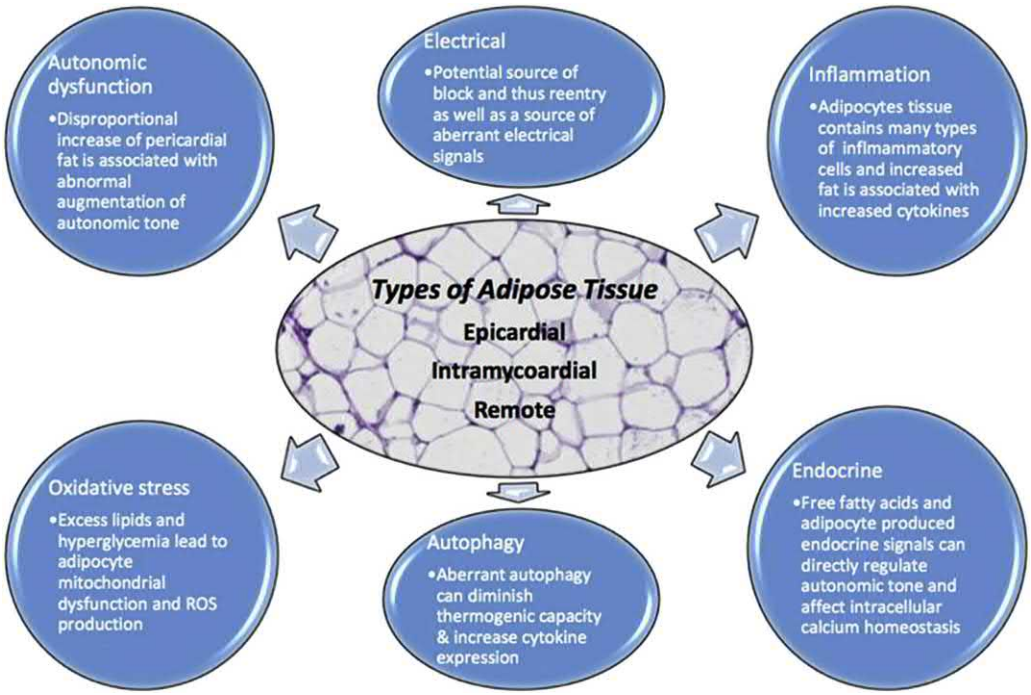

FIGURE 55.4 Effect of obesity on myocardium creating conditions for arrhythmias. *Reprinted from Pabon MA, Manocha K, Cheung JW, Lo JC. Linking arrhythmias and adipocytes: insights, mechanisms, and future directions. Front Physiol. 2018;9:1752.*

The classical paradigm postulates that the QRS amplitude in obese subjects is low, due to the insulation effect of the subcutaneous fat and the increased distance of the recording electrodes from the heart. However, conflicting results regarding the QRS amplitude in obesity have been reported. Frank et al. [108] showed that only 3.9% of obese individuals have low QRS voltage and the QRS voltage increases with increasing obesity. On the other hand, a decrease in QRS voltage was observed after weight loss [109,110].

Interestingly, obesity was shown to have different effect on the QRS voltage in premenopausal and postmenopausal women [111]. The values of the QRS electrical axis and the QRS voltage in lean premenopausal women were significantly higher than in the premenopausal obese women, and there was no significant difference between obese premenopausal women and postmenopausal women either lean or obese. It was suggested that this difference might reflect differences in electrogenesis in obese women in pre- and postmenopausal periods.

Obesity is frequently associated with other clinical conditions, such as diabetes mellitus, metabolic syndrome, hypertension, and sleep apnea [97]. Associated comorbidities and resulting underlying processes can contribute to the increased incidence of arrhythmias after menopause.

Summarizing, on one hand, women have more serious obesity, more visceral fat, more associated pathologies, such as diabetes mellitus, hypertension, sleep apnea, metabolic syndrome; however, they have less arrhythmia in premenopausal period. This difference decreases after menopause.

Left ventricular hypertrophy

LVH is a condition predisposing to ventricular arrhythmias and sudden cardiac death, as has been shown in epidemiological studies, clinical studies with hypertensive patients as well as in patients undergoing cardiac surgery [112–114].

LVH is defined as an increase in LVM. It can result from a hemodynamic overload, as is observed in hypertension or valvular diseases, the increase of LVM is also seen in cardiomyopathies, which represent a heterogeneous group of inherited and acquired diseases of myocardium (this topic is addressed in the part VII. “Cardiomyopathies and Inherited Disorders”).

The increase in LVM refers to the organ level of structural changes. Considering the physiological variability of LVM, additionally to the absolute LVM values, indexed measures of LVM are recommended for distinguishing normal and hypertrophic hearts (indexed to body surface, height, height powered to 2.7). In any of these measures, the normal values are sex specific, and the upper normal limits for women are lower.

It is obvious that it is not the simple increase in LVM that creates the arrhythmogenic substrate, but the underlying changes at the tissue and cellular levels affecting electric impulse generation and propagation. At the tissue level, the hypertrophic rebuilding of myocardium affects both cardiomyocytes and interstitium. As was shown in numerous studies on humans and animals, individual cardiomyocytes are enlarged in diameter and length and contain increased number of branching and connected cardiomyocytes, affecting consequently the electric impulse propagation [115–117].

Hypertrophied cardiomyocytes exhibit significant changes in electrical properties mainly during the repolarization phase of AP. The prolongation of AP, as well as a greater membrane capacitance in SHR, was observed, normalized to the control level during regression of LVH [118,119]. Animal experiments and clinical studies have demonstrated that the conduction velocity of hypertrophied myocardium is changed [120–122]. In LVH, there are significant changes in density and distribution of gap junctions, as well as in distribution and expression of the predominant isoform—connexin43 (Cx43) [123–125]. These changes create a solid basis for changes in electrical impulse generation and propagation. Changes in AP shape and duration are conditioned by alteration in the functional expression of depolarizing and repolarizing currents [for details see Refs. [127–132]].

The above described structural and functional alterations are not uniform across the hypertrophied myocardium. Additionally, the disproportion between the increased myocardial mass and coronary artery supply causes the underperfusion of hypertrophied myocardium creating additional areas of ischemic tissue. The heterogeneity of these changes and the mutual interplay of the involved factors can cause deviations from the normal ordered pattern of the electrical impulse propagation and create conditions for reentry.

Sex differences in LVH

There are differences in partition values of ECG diagnosis of LVH; however, the physiological differences in body size and LVM do not completely account for sex differences in QRS duration and voltage [126].

Women have lower prevalence of LVH compared to men with comparable blood pressure, and LVH become more frequent after menopause, suggesting a possible effect of sexual hormones. Women with LVH have better LV systolic function with comparable heart failure (HF) symptoms; on the other hand, HF in women is more likely to be due to diastolic dysfunction. Although LVH is less likely to develop in women, if LVH develops, it is a stronger risk factor for stroke and for HF [127].

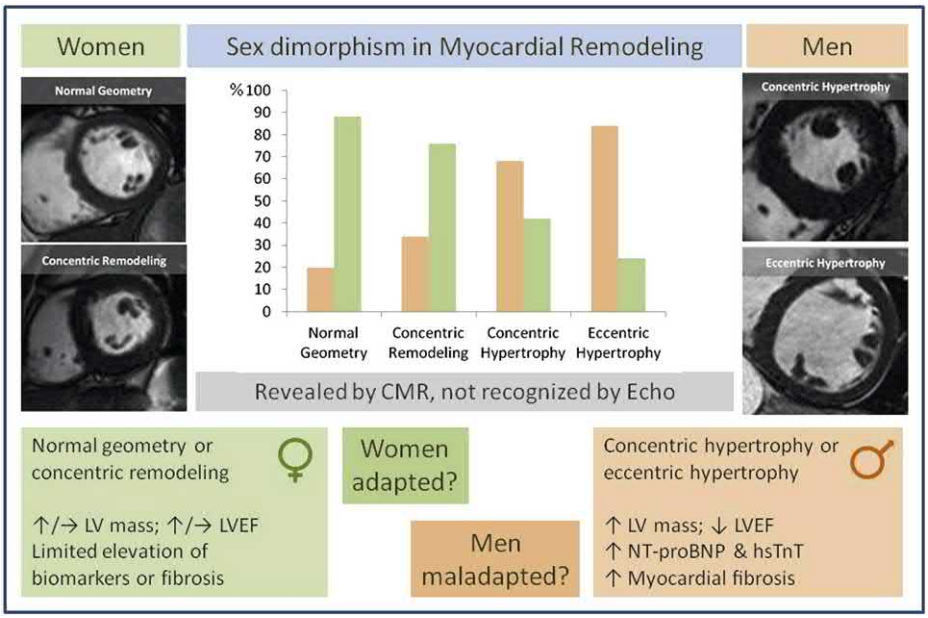

FIGURE 55.5 Sex differences in aortic stenosis: Cardiac magnetic resonance imaging captured sex dimorphism in the left ventricular remodeling pattern, missed by 2-dimensional echocardiography, and more adverse in men with more left ventricular dysfunction and myocardial fibrosis (focal and diffuse). Given equal valve severity, left ventricular hypertrophy appears more maladaptive in men. *CMR*, cardiac magnetic resonance; *hsTnT*, high-sensitivity troponin T; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *NT-proBNP*, N-terminal pro-brain natriuretic peptide. *Reprinted from Treibel TA, Kozor R, Fontana M, Torlasco C, Reant P, Badiani S, et al. Sex dimorphism in the myocardial response to aortic stenosis. JACC Cardiovasc Imaging 2018;11(7):962−73, with permission from Elsevier.*

Sex differences have been also observed in the effects of antihypertensive treatment and regression of LVH after treatment. The LVH regression is less effective in women and residual hypertrophy is more common in women despite effective blood control [128]; similarly, less regression of ECG signs of LVH in women was observed [129]. Patients who fail to achieve a reduction of LVH by antihypertensive treatment are more likely to suffer cardiovascular events [127]. Hypertensive women retained higher LV ejection fraction and stress-corrected midwall shortening in spite of less hypertrophy regression during long-term antihypertensive treatment [130]. Sex differences are described also in patients with aortic (Ao) stenosis. It was shown that severe Ao stenosis results in different phenotypes in women and men, despite the same age, Ao stenosis severity, and functional status [131].Women have a more favorable phenotype with higher prevalence of normal hypertrophy or concentric remodeling with higher LV ejection fraction, less focal fibrosis, and extracellular expansion. An open question is the effect of sexual hormones, since the majority of female patients in this study were postmenopausal and they do not receive hormone replacement therapy. Regarding the reverse remodeling after Ao valve replacement, men had superior reverse remodeling compared to women, but it was related to men's more serious LV remodeling before Ao valve replacement [132]. Sex differences in LVH in patients with aortic stenosis are illustrated in Fig. 55.5.

Some of the studies have reported different effect of different classes of antihypertensive drugs (for a review see, e.g., [134]). In the SAVE, AIRE, TRACE, and SOLVD trials, treatment with angiotensin-converting enzyme inhibitors resulted in similar benefit in women and in men. Benefit of treatment by beta-blocker was statistically significant in men but not in women. Few studies have suggested a possible additive effect of estrogen replacement therapy on LVM changes in hypertensive postmenopausal women. However, there are limited data on the effect of antihypertensive therapy on LVH specifically in women. Many of the major HF intervention trials did not include women or had only a small proportion of female patients.

Summarizing, women have lower prevalence of LVH compared to men with comparable blood pressure, and this difference is associated with better systolic function. This difference is reduced after menopause.

Fibrosis

Fibrosis is a part of pathological rebuilding of myocardium observed in number cardiac conditions, e.g., coronary artery disease and LVH. Fibrosis increases vulnerability of hypertrophied myocardium for arrhythmias. Advances in

imaging methods, such as cardiac magnetic resonance with late gadolinium enhancement, allow a noninvasive detection and quantification of fibrosis [133,134]. It has been shown that ventricular arrhythmias and sudden cardiac death correlate with the presence and extension of ventricular fibrosis [133].

Similar results were found also in animal studies. Al-Gburi S [135] showed that there are sex-specific differences in the progression of myocardial hypertrophy and fibrosis. Female spontaneously hypertensive rats have a delayed onset and less developed LV hypertrophy and fibrosis. This difference was not dependent on arterial pressure, but rather on sex-specific differences in renin–angiotensin system.

Fibrosis affects electrogenesis in several ways, affecting conduction as well as promoting triggers, thus having a critical role in creating conditions for reentry [133,136,137]. Fibrosis itself represents electrically inactive areas. Localized and diffuse fibrosis interspersed among cardiomyocytes isolate and insulate bundles of cardiomyocytes thus reducing connection between cardiomyocytes. The result is slowed and zig-zag electrical impulse propagation and increased anisotropy [138–140]. The effect of fibrosis is further affected by gap junction remodeling and changes in ion channels affecting the AP properties, producing dispersion of refractoriness among cardiomyocyte strands and promoting triggers. Additional proarrhythmic effect can have myofibroblast—cardiomyocyte coupling [141–143] and modulation of cardiomyocyte electrophysiology by paracrine factors secreted by myofibroblasts [144,145].

QRS-T patterns associated with structural changes—a link to arrhythmias?

In this chapter, several clinical conditions are presented that are associated with increased prevalence of ventricular arrhythmias. These conditions are associated with typical ECG patterns that are classically attributed to corresponding anatomical and structural changes.

The electrophysiological factors linking the structural changes to ventricular arrhythmias are altered electrical impulse generation and propagation. Naturally, the interest is focused on the QRS-T patterns that are associated with altered ventricular depolarization and repolarization, such as prolonged QT interval or fragmented QRS complex. However, simulation studies using computer simulation have shown that the QRS-T patterns reflecting altered ventricular activation go beyond the classical ECG interpretation. Another challenge is the interpretation of the controversial ECG results, and of the so-called false-positive or false-negative ECG results.

Myocardial infarction

The characteristic QRS changes in MI—the Q waves and ST segment deviations—are classically attributed to necrosis/scar (electrically inactive tissue) and to the "injury current"—the current flowing between areas with different values of resting transmembrane potential (ischemic and nonischemic). The possible effect of slowed conduction velocity is not considered in the interpretation of these changes. A simulation study showed that slowed impulse propagation in combination with areas of electrically inactive areas (necrosis, fibrotic scar) can result in a variety of ECG finding that are observed typically in patients with MI [146]. These changes include not only pathological Q waves and ST segment deviations in defined locations but also changes in QRS amplitude, the increase in QRS amplitude fulfilling ECG criteria for LVH, and electrical axis deviations that are classically attributed to other factors [147–149].

Left ventricular hypertrophy

The increased QRS voltage is considered to be a specific ECG sign of LVH, and it is interpreted as the effect of the increased LVM.

Simulation study, however, showed that the size of the left ventricle and the type of hypertrophy are not the main determinants of the QRS patterns, but it is the effect of the slowing in conduction velocity that results in a spectrum of QRS patterns including increased QRS voltage and duration, left axis deviation, prolonged intrinsicoid deflection, left bundle branch block, as well as pseudonormal ECG patterns. Additionally, the slowed conduction velocity results in QRS patterns consistent with changes described in LVH, even if the LVM is not increased [150,151].

Fibrosis

Classically, the main limitation of the ECG diagnosis of LVH is the height number of so-called false-negative results (the disagreement between the increased LVM and QRS voltage within normal limits) and resulting low sensitivity of ECG-LVH criteria. However, it was shown that diffuse myocardial fibrosis detectable in LVH interferes with ECG voltage measures, since myocardial mass and diffuse myocardial fibrosis have independent and opposing effects on QRS voltage. In reality, the ECG results earmarked as "false negative" reflect an important structural alteration—the increased proportion of diffuse myocardial fibrosis—a potentially arrhythmogenic substrate [152,153].

Obesity in women and the effect of menopause

Obesity is another example of selective interpretation of controversial findings. Traditionally, the ECG findings in obesity are related to the decrease in QRS amplitude, but opposite findings—the increased QRS voltage—are also documented [108–110]. Significant differences in QRS amplitude between obese and lean women were found in premenopausal women, while no difference in QRS amplitude was observed in postmenopausal obese and lean women [154]. The effect of obesity on ECG cannot be reduced only to the effect of the subcutaneous fat. Obesity is associated with profound structural changes of myocardium that are in women further modified by the hormonal status.

Obesity and comorbidities: diabetes mellitus, metabolic syndrome, and sleep apnea

Obesity is frequently associated with comorbidities, such as diabetes mellitus, metabolic syndrome, and sleep apnea. All of these clinical conditions are associated with increased risk of arrhythmias and conduction disturbances. Patients with sleep apnea showed significant QRS changes that are suggestive of depolarization sequence deterioration that might be indicative of considerable electrical remodeling [155]. Similarly, significant QRS changes were observed in patients with diabetes mellitus and metabolic syndrome. More importantly, subtle but significant differences in QRS amplitude were observed even in clinically healthy offspring of these patients suggestive of subtle changes in ventricular activation, potentially arrhythmogenic [156].

Current imaging methods provide deeper insights into the structural changes of the heart in cardiac pathology and represent a real challenge for electrocardiography. This stresses a need to go beyond traditional diagnostic categories and to reconsider the classical interpretation of QRS-T patterns in structural changes. Recognizing the contribution of impulse propagation slowing caused by structural alterations of ventricular myocardium to the morphology of QRS complexes is crucial for understanding links between structural changes, depolarization and repolarization processes, QRS patterns, and ventricular arrhythmias.

Conclusion

There are significant and clinically relevant sex differences in cardiac anatomy and structure, as well as in electrophysiology. Although these sex differences that can create arrhythmogenic substrate have been well documented, there are considerable gaps in knowledge on the pathophysiological mechanisms, as well as in diagnosis, prevention, and treatment of ventricular arrhythmias in women considering specifically these differences. Frequently, the results of clinical trials with predominantly male populations are extrapolated to women, the differences between men and women are assigned as "paradoxes," and consequently, women experience a longer time to diagnosis, later referral for invasive procedures, and a less intensive resource use patterns [157,158]. Decreasing these gaps in knowledge and consequently developing sex-specific diagnosis, prevention, and treatment of ventricular arrhythmias are challenges for both experimental and clinical cardiologists.

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Chapter 56

Catheter ablation of ventricular arrhythmias associated with structural heart disease

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Introduction

Increased incidence of sudden cardiac death (SCD) in patients with structural heart disease (SHD) is largely attributable to higher incidence of ventricular arrhythmias (VA) in this cohort [1]. Implantable cardioverter defibrillator (ICD) implantation has been the mainstay of treatment to reduce mortality due to VA [2]. While ICDs treat VAs, they do not influence their occurrence. Antiarrhythmic drugs (AADs) have only been partially beneficial in suppression of VA, and their use is partly limited due to their side effect profile [3,4]. Recurrent shocks via ICDs have significant psychological impact, reduced quality of life, and higher associated mortality [5,6].

VAs in the context of underlying SHD are invariably due to presence of scar tissue and resultant reentry due to intersperse viable cardiac myocytes [7,8]. Over the past few years, catheter ablation has emerged as a non-pharmacological adjuvant treatment modality for ventricular tachycardia (VT). Ventricular tachycardia ablation (VTA) has been shown to reduce recurrence of VT episodes [9], and recurrent VT after ablation in patients with SHD is associated with increased mortality [10,11]. The success rates are largely dependent on a combination of factors including underlying etiology, associated comorbidities and operator experience. VTA has become more popular and widely available with increased availability of advanced imaging modalities, electroanatomical mapping (EAM) systems, and further developments in ablation technologies. Catheter ablation of VT in patients with SHD has been shown to be a safe and effective approach to achieve long-term arrhythmia control in most patients. VTA has to be considered as an adjuvant and not exclusive to concomitant ICD and AAD therapies in patients with SHD and recurrent VAs.

There has also been a considerable sex difference in the incidence of VAs and consequently women significantly underrepresented in clinical trials involving VTA. This chapter will review these differences and highlight the main findings for VTA in women.

Sex differences in the incidence of sudden cardiac death

Earlier reported population studies have shown a higher incidence of SCD among men [12–14] with coronary heart disease predicting the risk of SCD in both sexes [15]. Women were also less likely to have a diagnosis of SHD prior to SCD [16]; and present in the majority with SCD as their first manifestation of heart disease [17]. In addition to traditional risk factors (age, diabetes mellitus, smoking), a history of depression and longer corrected QT interval were independent predictors of SCD in women [18]. This may in part explain women accounting for 70% of recorded cases of cardiovascular medication–related arrhythmias [19]. In one epidemiologic study, lifetime risk of SCD was noted to be 1 in 9 and 1 in 30 among men and women, respectively [13]. SCD risk was significantly lower in female athletes compared with their male counterparts [20].

In a recently published study on autopsy findings, causes of death and electrocardiographic risk markers in a large cohort of 5869 patients with SCD, women were considerably older at the time of SCD and more commonly had non-ischemic causes. ECG criteria for left ventricular

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(LV) hypertrophy with repolarization abnormalities were more commonly observed in women, but women were also more likely to have a normal ECG prior to that than men. Although the most frequently identified cause of death was ischemic heart disease (IHD) in both sexes, it was in a higher proportion in men and nonischemic cause in women [21] when compared with the other sex.

Indications for ventricular tachycardia ablation in patients with structural heart disease

VTA is recommended mainly to prevent or reduce further episodes in patients with recurrent symptomatic monomorphic VT despite AAD therapy, or when AAD therapy is contraindicated or not tolerated. In patients with IHD on amiodarone, catheter ablation is a preferred treatment option to escalating AAD therapy. VTA may be considered after single episode of sustained monomorphic VT in patients with IHD and ICD to reduce the risk of recurrent VT or ICD therapies. Catheter ablation is indicated when premature ventricular contractions (PVCs) are suspected to be contributing to a cardiomyopathy, limiting optimal biventricular pacing in nonresponders or when they trigger ventricular fibrillation (VF) and for whom AADs are ineffective, not tolerated, or not preferred for long-term therapy [22]. Some of the contemporary indications for ventricular tachyarrhythmia ablation in clinical practice are summarized in Table 56.1.

Tools used for ventricular tachycardia ablation

Technological advances over the past two decades with development of EAM systems and improved catheter technology have been contributory to much wider use of VT ablation in clinical practice.

EAM system helps with creation of a virtual cardiac chamber shell with point by point voltage and activation times and nonfluoroscopic catheter visualization [23,24]. It helps define localized areas of cardiac chamber being assessed in terms of substrate (viable, scar, or intermediate) and electrical activation (Fig. 56.1). EAM system also helps define tachycardia mechanism more elegantly in the case of reentrant tachycardias.

There are three main types of EAM systems currently available for use in ablation of VAs. Carto was the first EAM system to be developed and has been extensively studied in patients with SHD. Over the past two decades, it has undergone further changes with current version being CARTO 3 (Biosense-Webster, Diamond Bar, CA). CARTO system uses low-energy, nonhomogeneous electromagnetic fields emitted from three coils located in a triangular pad placed under the patients table, magnetic sensor at the catheter tip, and software to evaluate the magnetic field strength and orientation to localize catheter in space accurately. Six electrode patches are placed on the patients' chest to evaluate current emitted from different catheter electrodes. Latest version utilizes both magnetic and impedance data for accurate localization of the catheter. Fast anatomical mapping mode can be used for continuous acquisition of points by a simple movement of a catheter in the cardiac chamber to be assessed. The EnSite Precision system (Abbott Laboratories, Abbott Park, IL) former versions being EnSite Velocity and EnSite NavX (St. Jude Medical, St. Paul, MN) uses voltage and impedance measurements to localize diagnostic and ablation catheters. The relatively newer EAM Rhythmia HDx mapping system (Boston Scientific, Marlborough, MA) similarly uses both magnetic- and impedance-based methods for catheter localization. Data acquisition is made using a 64-pole mini basket catheter with closely spaced electrodes.

Over a period of time, EAM system's ability to create high-quality maps has largely been aided by development of high-density mapping using multielectrode catheters

TABLE 56.1 Some of the contemporary indications for ventricular tachyarrhythmia ablation in clinical practice.

Indications for VTA in structural heart disease
• Recurrent symptomatic monomorphic VT despite AAD therapy, or when AAD therapy is contraindicated or not tolerated
• Recurrent monomorphic VT despite chronic amiodarone therapy; catheter ablation is recommended in preference to escalating AAD therapy
• VT storm refractory to AAD therapy
• First episode of monomorphic VT; catheter ablation may be considered to reduce the risk of recurrent VT or ICD therapies
• PVC focus ablation when monomorphic; triggers VF or suspected to be contributing to cardiomyopathy or limiting optimal BiV pacing and in whom AADs are ineffective, not tolerated, or not preferred for long-term therapy

AAD, antiarrhythmic drug; *BiV*, biventricular; *ICD*, implantable cardioverter defibrillator; *PVC*, premature ventricular contraction; *VF*, ventricular fibrillation; *VTA*, ventricular tachycardia ablation; *VT*, ventricular tachycardia.

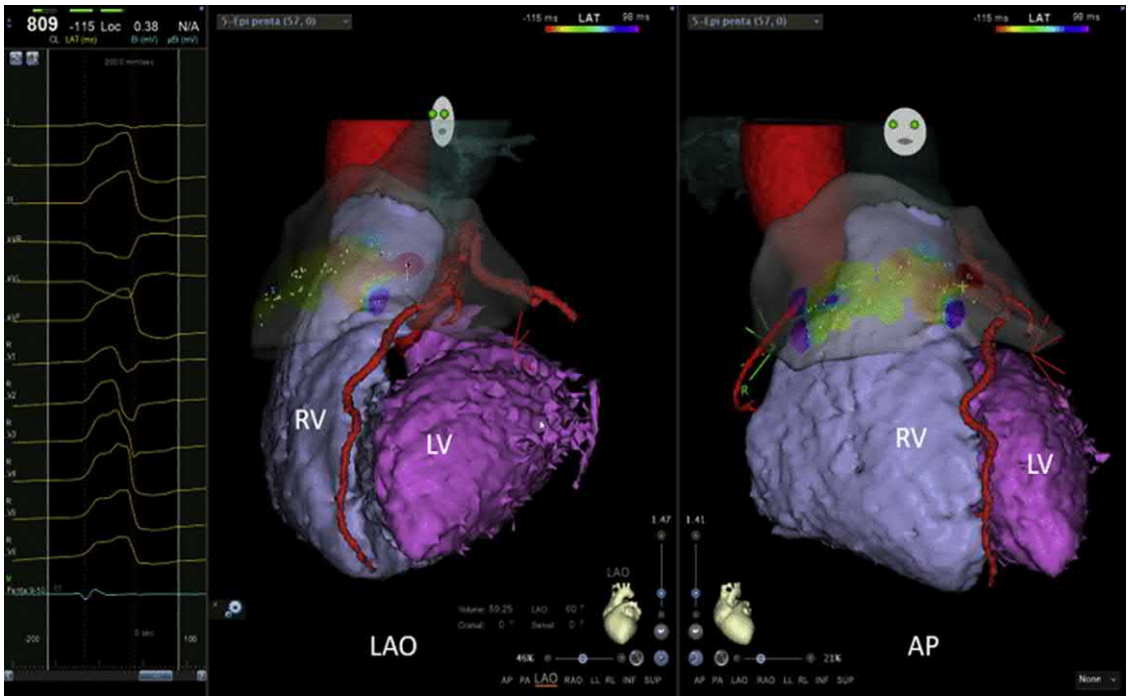


FIGURE 56.1 3D electroanatomical map created using CARTO and integrated with a 3D reconstruction of a cardiac CT image using CARTO merge feature. The panel on the left depicts cardiac contour in left anterior oblique (LAO) view including the coronaries, FAM of the epicardial space, activation, and pacemap in the region of right ventricular outflow tract. Note red dot denoted the region of earliest activation (as well as the best pace map when patient in sinus rhythm) and also area of successful ablation of the right ventricular outflow tract ectopic focus anteroseptally. This focus was ablated sequentially from an endocardial surface, followed by an epicardial ablation for a successful outcome. Panel on the right shows this integrated EAM in an anteroposterior view. Close proximity of the ablated site to the septal branch of LAD can be better appreciated in this view. *EAM*, electroanatomical mapping; *FAM*, fast anatomical mapping; *LAD*, left anterior descending.

with small electrodes, short interelectrode spacing, and noncontact data acquisition in some cases [25]. Use of EAMs has facilitated reduction in fluoroscopic times and radiation exposure for patients as well as physicians alike, and complex steps like transeptal puncture were shown to be feasible using EAM without fluoroscopy [26].

Remote navigation systems have been developed on the premise that it would provide better precision movement of ablation catheter and improve outcomes by enabling more effective lesions [27] (Fig. 56.2). Significantly, lower fluoroscopic times were achieved with comparable outcomes when remote magnetic navigation system was used for ablation of ischemic VT [28].

Over years, open irrigated catheters are used as standard when ablating VAs due to better and deeper lesions that can be created with their use. Use of smaller tip catheters with hypotonic saline irrigation, simultaneous unipolar or bipolar ablation delivered by two catheters, and needle ablation using an intramurally paced retractable needle from catheter tip are currently under evaluation for ablation of deep intramural focus [22].

Development of catheters with contact force sensors is a major breakthrough in the recent years [29]. Use of these catheters helps ensure adequate contact with the tissues both during mapping and ablation, optimal contact force during ablation being >10 g [30].

Technique of ventricular tachycardia ablation

Viable myocytes interspersed with areas of fibrosis form channels for slow and resultant diastolic conduction that facilitates circuits for reentry. The etiology of fibrosis is underlying IHD with previous myocardial infarction and scar formation in majority of the patients. Others include nonischemic cardiomyopathy (NICM), hypertrophic cardiomyopathy, inflammatory and infiltrative conditions, previous cardiac surgery with resultant scar formation, and arrhythmogenic right ventricular dysplasia. Successful identification of underlying arrhythmic substrate would involve defining areas of scar and reentrant channels. There are several strategies for mapping these areas. Some of these are described in the following:

(a) Substrate mapping

Voltage mapping allows identification of areas of scarred myocardium and viable areas within the scar. This is based on the observation that viability of myocardium

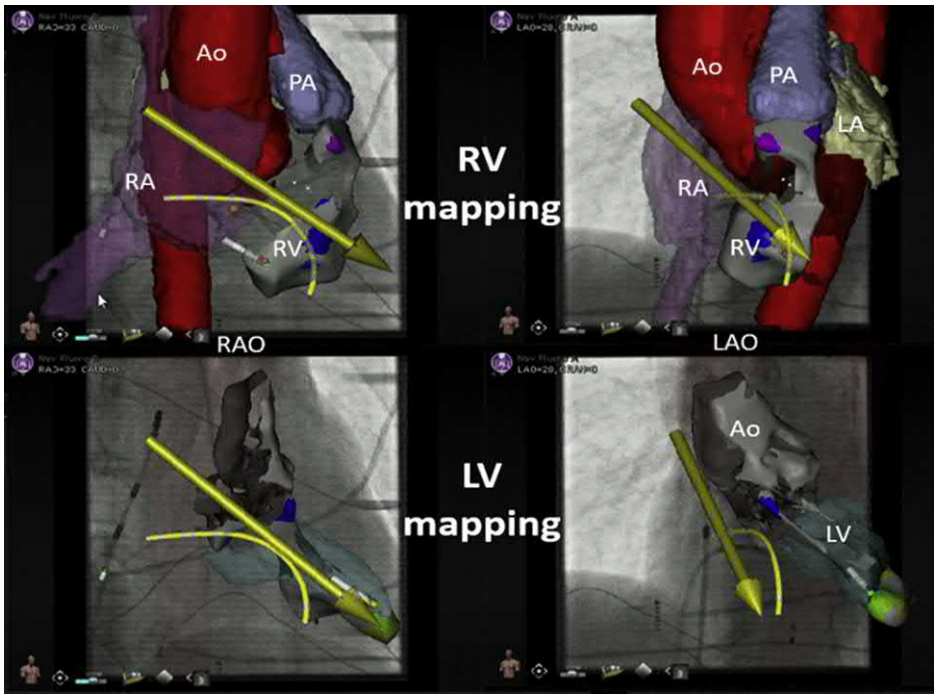


FIGURE 56.2 The superimposition of 3D electroanatomical map using CARTO and RMT on fluoroscopic reference images. Panel above shows right atrial and right ventricular FAM. Tip of the mapping catheter is visualized along with the yellow arrow, which depicts the direction of the magnetic vector used during the remote-controlled catheter navigation. The magnetic navigation system (Sterotaxis Inc., St. Louis, US) was used in conjunction with the cardio drive system. The direction of the catheter tip was controlled by moving the yellow vector in various directions and cardio drive allowed advancement and retraction of the catheter. Panel below depicts the LV mapping. Note retrograde LV access was obtained as evidenced by the aortic root FAM. Also note integration of the 3D electroanatomical map with preprocedure 3D reconstruction image from the cardiac MRI. This integration allows for real-time catheter visualization on the fluoroscopic reference images. *FAM*, fast anatomical mapping; *LV*, left ventricular.

can be defined by local sensed electrical activity with >1.5 mV bipolar sensed signals recorded from >95% of viable myocardium. Mapping is performed when patient is in native or paced rhythm. Using EAM, local signals from the endocardium and/or epicardial surface are recorded. Normal endocardial signals identified as bipolar voltage of >1.5 mV, scar areas with bipolar voltage signals of <0.5 mV, and intermediate/border zones with voltages between 0.5 and 1.5 mV [31–34] and are displayed in a color-coded fashion. Traditionally, viable normal myocardium represented by purple for areas with values of >1.5 followed in the descending order by blue, green, yellow, and red (representing dense scar) being < 0.5 mV. When defining these areas, it is essential to ensure adequate contact with endocardium, and this can be assessed either by catheter manipulation or by information obtained when contact force catheters are used. While performing substrate mapping areas with abnormal voltage signals, late potentials (low amplitude signals seen after QRS) that are usually classified as early-, mid-, or late diastolic (presystolic) signals depending on their timing and fractionated signals are all tagged. Areas of continuous electrical activity are also tagged [35,36]. These are the areas that represent slow or diastolic conduction, which are essential for formation of reentrant circuits.

(b) Pace mapping (Fig. 56.3)

The paced QRS is the resultant activation of ventricular myocardium from the point of pacing. During VT, QRS morphology is the resultant activation of myocardium from a focal activation point (in case of focal tachycardias) or an exit site in case of reentrant VT. During pace mapping, pacing is carried out from various regions of the endocardium and resultant 12-lead ECG compared with one acquired during tachycardia or ectopy. Pacing from the isthmus of a reentrant circuit can produce a QRS morphology identical to tachycardia (12/12-lead match). In case of a perfect pacemap, stimulus-QRS (S-QRS) indicates proximity of pacing point to the exit site. A short S-QRS interval is seen when the pacing site is in close proximity to the exit site, and a long interval is seen with other areas of isthmus and protected regions of slow conduction within the circuit, including adjacent bystander sites [37].

When pacing, a stimulus that fails to capture the ventricles but terminates tachycardia implies an isthmus site and hence a suitable target for ablation.

(c) Entrainment mapping

During tachycardia, pacing stimuli are delivered at a cycle length slightly shorter than VT cycle length. Once

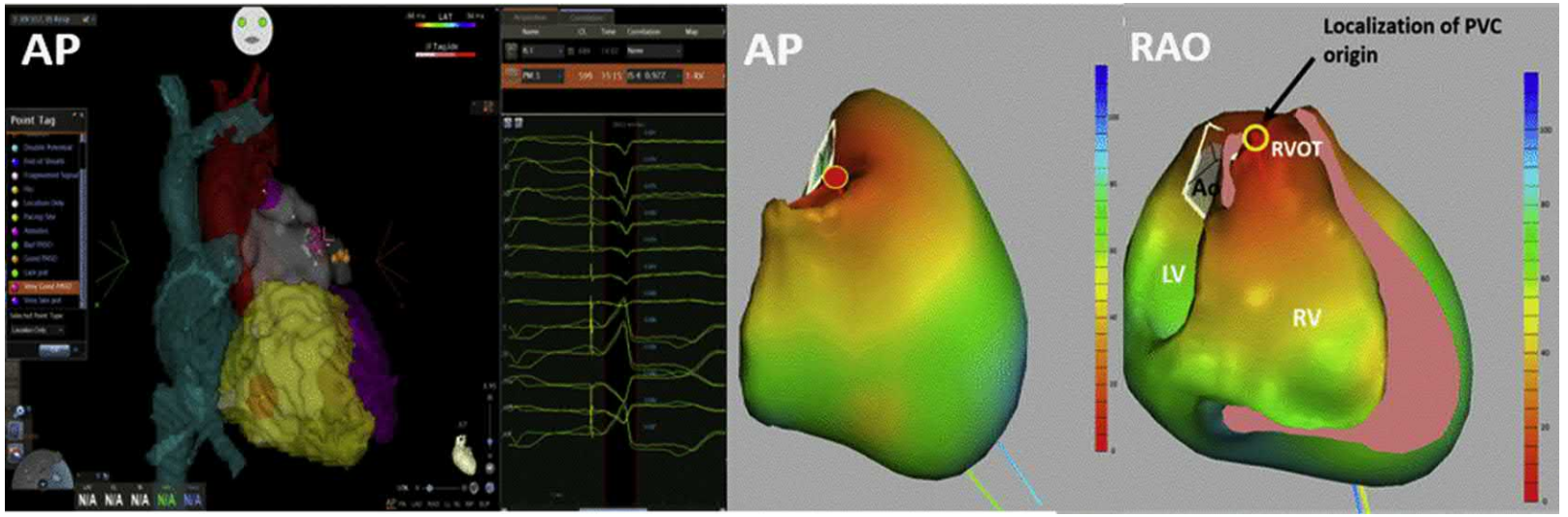


FIGURE 56.3 Demonstrated on the right is the image obtained from "View into Ventricular Onset" (VIVO), a noninvasive ECGI (electrocardiogram imaging) tool that localizes the site of earliest ventricular activation. VIVO images are created by using a 3D image of the patient's torso to register electrode position and images obtained from cardiac CT/MRI in a patient-specific myocardial mode. VIVO images are shown in the anteroposterior and right anterior oblique views. Note earliest region of activation is highlighted by the red dot and corresponds to anteroseptal aspects of the right ventricle. Shown on the left is the integrated image from CARTO endocardial electroanatomical mapping and preprocedure 3D reconstruction image from cardiac MRI from the same patient. Pace mapping was carried out to identify areas with best 12-lead match to the clinical PVC. Light purple dots represent areas with best 12-lead match and area of successful ablation. These are found in cloe proximity to His bundle region highlighted by orange dots. This para-Hisian region identified by electroanatomical endocardial mapping seems to correspond to the area predicted by the VIVO map created noninvasively.

ventricular capture is confirmed, the following four criteria are used to define the relation of the site being paced to the tachycardia circuit: (1) paced QRS morphology, (2) S-QRS interval, (3) electrogram-QRS interval (EGM-QRS), and (4) postpacing interval (PPI) [38].

Entrainment that results in ventricular activation from the reentry exit site results in a paced QRS morphology, which is identical to the VT morphology, and this is defined as entrainment with concealed fusion [39]. This occurs when entrainment is carried out from inner loop, isthmus, or adjacent bistandard sites (Fig. 56.4). Concealed fusion occurs as a result of collision between orthodromic and antidromic wave fronts within the critical isthmus, resulting in local fusion that is not detectable on 12-lead ECG. Entrainment with manifest fusion occurs when pacing is carried out from outer loop or remote bystander sites, and the resulting QRS morphology is different from tachycardia due to manifest fusion between orthodromic and antidromic wave fronts. S-QRS interval is inversely proportional to the distance of the paced site to the reentry exit site. The S-QRS interval is very short when pacing is carried out at outer loop or remote bystander sites. EGM-QRS interval represents the time between mapping site of activation to QRS complex. Inner loop and isthmus sites demonstrate a near equal stimulus QRS and EGM-QRS intervals, whereas this varies with remote bystander and outer loop sites. PPI is measured from the last pacing stimulus to the first spontaneous electrogram recorded on the ablation catheter. Entrainment from a site within the tachycardia circuit results in a PPI-VTCL of $\leq$30 m. PPI-VTCL is $>$ 30 ms in case of adjacent or remote bystander sites [38,40].

(d) Activation mapping

An activation map visualizes the electrical activation sequence relative to a timing reference signal which can consist of either an endocardial EGM from a fixed diagnostic catheter or a surface QRS complex. The window of interest (WoI) is set as time constant traditionally calculated as 20 ms less than tachycardia cycle length. Typically, the QRS complex corresponds to the midpoint of the WoI to allow visualization of the diastolic activation at the beginning and the end of the WoI. During mapping, each point is assigned as being early or late compared with the reference. Earliest regions of activation correspond to electrical source of VT QRS. This is area of reentrant exit site in case of reentrant tachycardias or alternatively a discrete site of abnormal impulse formation in case of automatic or triggered rhythms. Quality and reliability of the activation map is dependent on the number of acquired points. This was usually a time-consuming exercise when contact mapping was used during tachycardia. However, these have now become time-efficient and feasible with development of high-density mapping with small mapping electrodes (e.g., Orion basket of Rhythmia, HD grid of Abbott, or PentaRay of CARTO3).

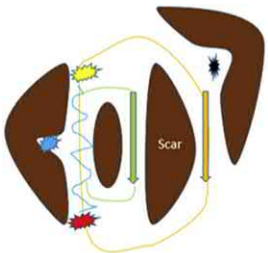
Patient specific approach to ventricular tachycardia ablation

One rule does not apply to all when VT ablation is being considered. Approach has to be very much tailored to each patient addressing specific considerations. VTA strategies in SHD are summarized in Table 56.2.

Preprocedure consideration

Several issues need to be addressed prior to procedure. Etiology of underlying cardiac disease needs to be well defined with detailed knowledge of patient's coronary arteries and LV ejection fraction. Any ongoing myocardial ischemia needs to be treated prior to VTA. Defining nature of underlying cardiomyopathy also helps in anticipation of possible mapping strategies including endocardial, epicardial, or both as in most cases with underlying NICM.

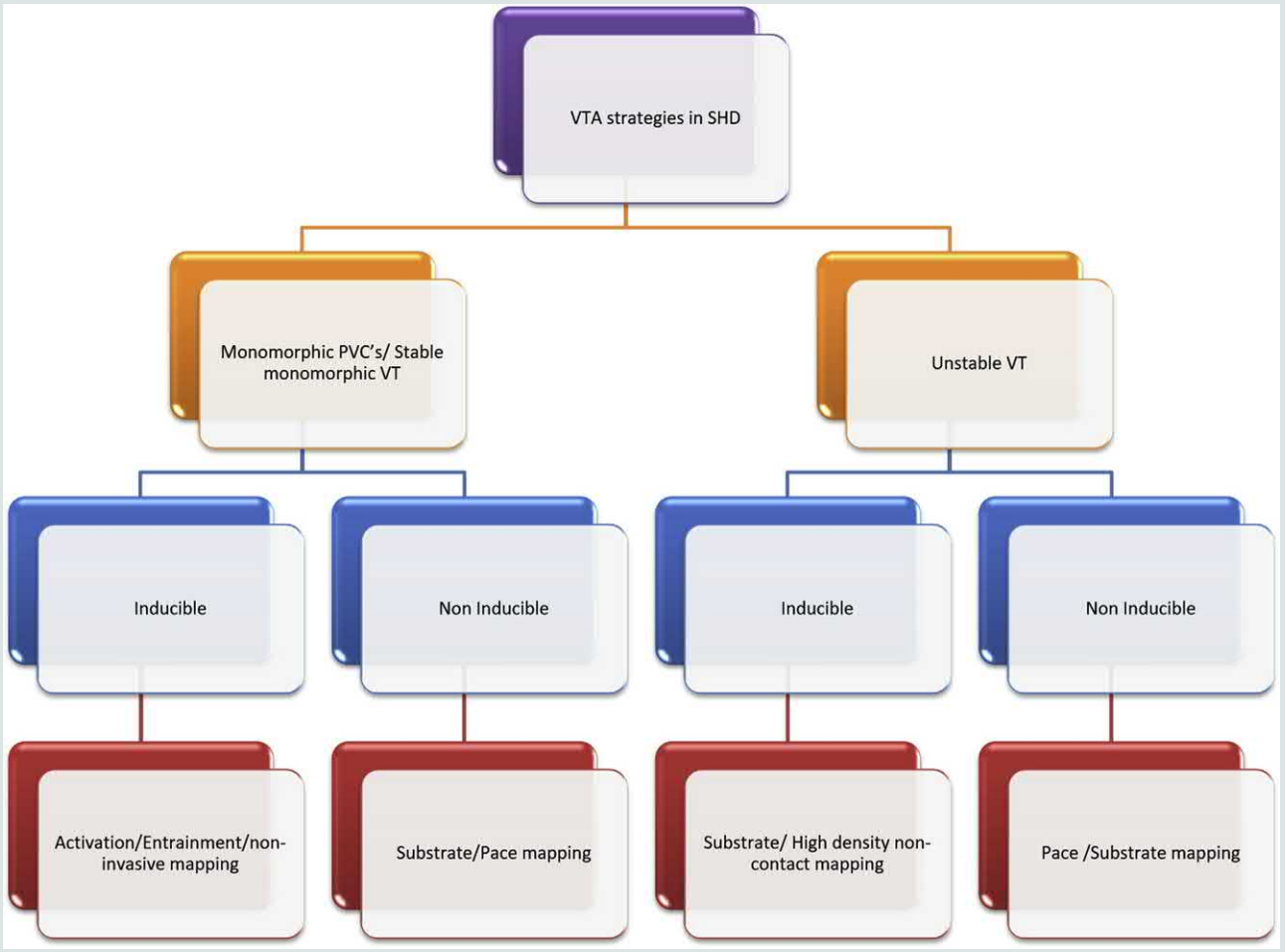
Antifailure medications optimized prior to VTA including rigorous management of decompensated heart



Variable	Entry	Exit	Isthmus	Inner loop	Outer loop	Adj BS	Remote BS
PPI-TCL (ms)	≤30	≤30	≤30	≤30	≤30	>30	>30
St-QRS to egm-QRS (ms)	≤20	≤20	≤20	≤20	Variable	>20	>20
St-QRS/TCL (%)	51-70	≤30	31-50	>70	≤30	51-70	≤30
Fusion	Concealed	Concealed	Concealed	Concealed	Manifest	Concealed	Manifest

FIGURE 56.4 Representation of an entrainment mapping of a reentrant ventricular tachycardia (VT) circuit within the areas of dense scar tissue is shown. Activation sequence is represented by arrows. Isthmus (represented by *blue and orange lines*), entry site (red), exit site (yellow), inner loop (green), outer loop (orange), remote bystander (black), and adjacent bystander (blue) all form a part of the VT circuit. Characteristics of entrainment from each of these sites is represented using postpacing interval (PPI), tachycardia cycle length (TCL), stimulus (St), QRS (earliest surface QRS), intracardiac local electrogram (egm) signals, and their intervals are represented in the adjacent table.

TABLE 56.2 Various etiological causes of ventricular tachyarrhythmias in structural heart disease. Possible underlying mechanism, substrate, best ablation strategies, and approach along with sex-specific differences are described.



failure and correction of electrolyte imbalance. Where possible, antiarrhythmic medication needs to be discontinued for at least five half-lives prior to procedure; however, this may not be feasible in case of unstable patients.

Imaging prior to VTA: An echocardiogram should be performed in all patients prior to VTA. During ECHO LV function assessment, defining valvular heart disease, presence of aneurysmal, and akinetic LV segments should be well defined. Presence of LV thrombus precludes to endocardial approach, necessitating epicardial access if VTA contemplated for incessant VT.

Additional three-dimensional imaging with CT or cardiac MRI is desirable to define cardiac anatomy, including detailed description of potential scar areas including perivalvular regions [41–43]. Their image integration with EAM system has been shown to be feasible [44–47] and can be done using 2D Digital Imaging and Communications in Medicine (DICOM) tomographic information generated from the previous imaging. Caution needs to be exercised when integrating these images as improper registration of optimal alignment can lead to malalignment resulting in misinterpretation of information obtained from imaging. Cardiac CT has the disadvantages of high radiation dose and contrast use, and presence of a cardiac device (as with most patients with severe LV systolic dysfunction) may preclude CMR in patients with non-MRI compatible devices or cause image distortion [48]. In patients with inflammatory conditions, F-fluorodeoxyglucose–positron emission tomography (FDG-PET) may be useful for the assessment of ongoing inflammation [49].

Noninvasive scar localization prior to VTA has increasingly been used in the clinical practice. Late gadolinium enhancement CMR (LGE-CMR), late iodine-enhanced MDCT, and nuclear cardiac perfusion scans have all been used for this purpose [50–53]. However, LGE-CMR is the preferred imaging modality for myocardial scar detection (in the absence of image distortion from the presence of a cardiac device). Dense LGE areas represent the scar, whereas interspersed continuous intermediate signal regions represent areas of slow conduction zones during VT. Using noninvasive scar localization prior to procedure has been shown to improve procedural success. More recently, noninvasive localization of earliest ventricular activation during ventricular ectopy or tachycardia is made possible using ECGI (ECG imaging) technique. Myocardial and torso contours are generated from cardiac CT or MRI and are merged with a 3D image of the patient torso with ECG electrodes. The 12-lead ECG is then incorporated, and a model of ventricular activation is generated, with site of earliest activation marked [54].

Alternative noninvasive approach in development is the use of 3D computational virtual heart model developed based on the information obtained from delayed enhancement CMR. Computerized model of the ventricle is created defining the infarct, gray zone, and normal myocardial tissue segments. Model VT circuits are simulated and ablation targets determined using simulated nonconductive ablation lesions in the virtual heart. This information can then be integrated with the 3D EAM system during the procedure to help identify the possible ablation targets [55].

Availability of 12-lead ECG taken during clinical tachycardia is of utmost importance in patients undergoing VTA. This helps to identify possible location of area to be targeted for ablation. A positive or negative precordial concordance suggestive of basal ventricular or apical origins, respectively. Similarly, superior or inferior QRS axis is suggestive of inferior wall or anterior/outflow tract origins, respectively. BBB morphology of VT is defined based on the terminal QRS forces in lead V1. RBBB morphology with positive terminal QRS forces in lead V1 is suggestive of LV origin, and LBBB with negative terminal QRS forces in V1 is suggestive of RV/LV septal origins. Wide QRS with pseudodelta wave is suggestive of an epicardial origin. Predictors of possible epicardial origin include QRS duration of over 200 ms, pseudodelta wave $>$ or $=$ 34 ms, intrinsic deflection time $>$ or $=$ 85 ms, and shortest RS complex $>$ or $=$ 121 ms [56]. The VIVO system allows the calculation of the exit site or site of focal origin of a VA by combining the 12-lead morphology, the exact position of the 10 ECG leads, and the individual cardiac and torso anatomy. Accuracy of prediction has been demonstrated to be $>$98% as compared with expert readers and can differentiate endo- from epicardial sites in patients with a scar burden of $<$10% (Fig. 56.3).

Defibrillator device needs to be programmed appropriately with tachy therapies being switched off prior to procedure.

Procedural recommendations

Sedation strategy during VTA ranges from light sedation to general anesthesia including conscious sedation and deep sedation. This has to be very much based on patient requirements, hemodynamic stability, underlying comorbid conditions, and the expected duration of the procedure. Epicardial access may necessitate general anesthesia, whereas ablation of a PVC focus may need only minimal sedation. Most procedures are carried out using conscious sedation with short-acting sedatives and analgesics. Arrhythmia inducibility versus patient comfort needs to be assessed when making an appropriate choice of sedation strategy [57].

It is advisable to obtain ultrasound-guided vascular access to reduce vascular complications during VTA [58].

Appropriate anticoagulation using heparin needs to be undertaken when the left heart is accessed during VTA with regular boluses of unfractionated heparin ranging between 50 and 100 IU per kg body weight to maintain an activated clotting time between 250 and 350 during the procedure to avoid clot formation and subsequent thromboembolic events.

A suitable mapping strategy needs to be adopted during procedure based on the tachycardia characteristics, including inducibility, reproducibility, sustainability, and hemodynamic tolerability.

In patients with significant LV dysfunction, use of LV assist devices may be considered for the duration of the procedure.

Postoperative care and follow-up

Postprocedure anticoagulation may be reversed by the use of protamine for vascular sheath removal. Manual compression or application of a temporary purse string suture can be employed for hemostasis postsheath removal. Stable patients are monitored for 24 h, whereas unstable patients may need continued support in intensive care unit.

Sex differences in ventricular tachycardia ablation outcomes

Overall, there are little data on sex-specific outcomes of VTA, and techniques applied are generally the same irrespective of the sex of the patient. A few reports have focused on sex difference recently.

Santangeli and colleagues reported early postmortality data in a cohort of patients undergoing radiofrequency catheter ablation for VT due to underlying SHD [59]. Majority of these patients were diagnosed with ischemic cardiomyopathy (ICM), whereas patients with NICM included those with myocarditis, sarcoidosis, congenital heart disease, arrhythmogenic right ventricular, hypertrophic, valvular, toxin-induced, chagasic, and idiopathic dilated cardiomyopathy.

Early mortality (EM) defined as mortality occurring within 1 month following index procedure including in-hospital and early postdischarge mortality was noted to be 5% among 2061 patients from 12 centers. Overall mortality was reported as 13% at 1 year. Over 50% of these patients with EM died before hospital discharge. Cause of death was HF related in majority, VT storm, major bleeding, and thromboembolic events among others. Low LVEF, chronic kidney disease, VT storm, unmappable VTs, and postprocedure recurrence of VT were factors associated with EM. The majority of patients undergoing VTA were males; however, there was no difference in EM or late mortality incidence between the sexes.

In the same cohort of patients, Frankel and colleagues reported 70% freedom from VT recurrence, with an overall transplant and/or mortality rate of 15% at 1 year [60]. Freedom from VT recurrence is associated with improved transplant-free survival, independent of heart failure severity. ICM and higher EF were associated with lower probability of VT recurrence. Highest probability of VT recurrence was associated with increasing NYHA class, female sex, $\geq$2 antiarrhythmic drugs, electrical storm, deferred postablation testing, and any sustained monomorphic VT inducible after ablation. Higher recurrence rates were noted with NICM compared with ICM.

Compared with men, women were younger, with higher LV ejection fraction and less VT storm and higher incidence of NICM. Women were more likely to have recurrent VT than men. Women and men with NICM had similar rates of VT recurrence. However, women with ICM were more likely to have recurrence than men with ICM.

While there was no difference in complications and early and late mortality following VTA for SHD between sexes, female sex was associated with higher probability of VT recurrence at 1 year post-VTA. Sex differences in VTA outcomes based on etiology and as observed in some of the clinical trials are summarized in Tables 56.3 and 56.4, respectively.

Future outlook

VT ablation has become available to a much wider population due to recent technological advancements. Continued technological developments including noncontact mapping, newer methods to approach ablation targets with irrigated needle tip catheters, and noninvasive focused stereotactic radiation offer promise. Further research into sex differences in ventricular arrhythmia incidence and management outcomes will help develop better management strategies in women.

TABLE 56.3 Some of the select trials of ventricular tachycardia ablation highlighting sex representation in these trials.

Etiology	Tachycardia mechanism	Substrate	Ablation strategies	Gender differences
IHD	Reentry	Regions of prior infarct	Mostly endocardial	Higher VT recurrence rates in women; no difference in complication rates
NICM	Reentry and focal	Intramural and epicardial	Endo- and epicardial	VTA equally effective no difference in complication rates
Sarcoidosis	Scar-related reentry	Intramural locations	Endo and or Epicardial access	No reported difference in VTA outcomes
HCM	Reentry	Mostly in septal regions	Endo and or Epicardial	No reported differences in VTA outcomes
ARVD	Reentry	Subtricuspid and RV outflow tract regions	Mostly epicardial	Male sex is a risk factor for arrhythmia; no reported difference of VTA outcomes
CHD previous surgery	Reentry around surgical scar sites	Between anatomical barriers and surgical incisions or patch material	Mostly endocardial	No reported differences in VTA outcomes

ARVD, arrhythmogenic right ventricular dysplasia; *CHD,* congenital heart disease; *HCM,* hypertrophic cardiomyopathy; *IHD,* ischemic heart disease; *NICM,* nonischemic cardiomyopathy; *VT,* ventricular tachycardia; *VTA,* ventricular tachycardia ablation.

TABLE 56.4 Best ablation strategies during ventricular tachycardia ablation based on tachycardia characteristics and current available mapping techniques.

Study	Design	Number and cohort	Outcomes	Gender representation
SMASH VT [61]	RCT VTA + ICD vs. ICD	128-ICM	Lower incidence of appropriate ICD therapies in VTA group	Women constituted less than 20% of study population
VTACH [62]	RCT VTA + ICD vs. ICD	107-ICM	Longer duration to recurrence to VT/VF in VTA group	Women constituted 7% of study population
HELP-VT [10]	Prospective	227-NICM and ICM	Lower VT free survival in NICM group	Women constituted less than 20% of study population
VANISH [63]	RCT	259-ICM	Composite of death, VT storm, and ICD therapies lower in VTA group	Women constituted less than 10% of study population
Multicentre Thermacool VT Ablation Trial [9]	Observational	231-ICM	Freedom from recurrent VT at 6 months achieved in 53%	Women constituted 11% of study population
IVTCC [11]	Retrospective	2061-ICM and NICM	Recurrence rates: NICM > ICM	Women less than 15% of study population; recurrence rates higher among female patients

ICD, implantable cardioverter defibrillator; *ICM,* ischemic cardiomyopathy; *NICM,* nonischemic cardiomyopathy; *TCT,* randomized controlled trial; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia; *VTA,* ventricular tachycardia ablation.

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Chapter 57

Sex differences in idiopathic ventricular arrhythmias

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Introduction

Idiopathic ventricular arrhythmias (VAs), including monomorphic ventricular tachycardias (VTs) and premature ventricular contractions (PVCs), most commonly arise from the right ventricular (RV) outflow tract (OT) [1−5]. Left ventricular (LV), verapamil-sensitive, fascicular VTs mainly originating from the LV inferoseptum are also classified into idiopathic VTs [1−5]. Furthermore, previous reports have demonstrated other origins of VAs, such as the LVOT, LV epicardial sites, around the mitral annulus (MA), and tricuspid annulus (TA) [1−5]. It has been becoming clear that VAs arising from papillary muscles and those from the ventricular crux also occur in patients with no structural heart disease [6−10]. Although the characteristics of each VA were reported in those studies, few studies have examined the sex differences in idiopathic VAs systematically or sufficiently. This article provides that information up to the present.

Sex differences in the various types of idiopathic VAs

Two studies have examined the sex differences in idiopathic VAs with a relatively large number of patients thus far [4,5]. Nakagawa et al. reviewed the sex differences in idiopathic VTs with an analysis of a total of 748 patients with idiopathic VTs from their own series and 68 articles [4]. In this study, VTs were defined as >3 consecutive PVCs. The VT origin was determined by the electrocardiograms and an electrophysiologic study, and the VTs were divided into three types: RVOT (RVOT-VT), LVOT (LVOT-VT), and LV septum (also known as verapamil-sensitive VAs; LV septum-VT) VTs. The sex characteristics of these three types of idiopathic VTs are shown in Table 57.1. Among 464 patients with RVOT-VTs, there were more females than males (male/female ratio, 0.49). In 227 patients with LV septum-VTs, males prevailed over females (male/female ratio, 3.37), whereas LVOT-VTs were distributed almost equally between males (n = 33) and females (n = 24). With the analysis of the age distribution in 419 patients from 51 studies, the highest incidence of RVOT-VTs occurred in the third to fifth decade of life in both males and females (males, mean 43.5 ± 18.7 years; females, mean 40.9 ± 13.8 years; Fig. 57.1). LV septum-VTs occurred at a younger age in both males and females than did RVOT-VTs ($P < .0001$ vs. RVOT-VT; Fig. 57.2). LV septum-VTs occurred at a younger age in females (25.7 ± 12.0 years) than males (33.0 ± 13.9 years; $P < .005$).

Tanaka et al. retrospectively examined the sex and age differences in idiopathic VAs in 625 consecutive patients with symptomatic, drug-resistant idiopathic VAs (315 males and 310 females; mean age, 54 ± 17 years; 218 VTs and 407 PVCs) who underwent catheter ablation in a single center [5]. In this study, the VA origins were defined as the site where the earliest ventricular activation was recorded and/or a perfect pace map was obtained. According to the VA origin, the patients were divided into five groups: (1) OT-VAs, consisting of RVOT-VAs and LVOT-VAs, (2) inflow tract (IT)-VAs, consisting of TA-free wall (FW)-VAs, IT-septum-VAs, and MA-FW-VAs, (3) LV septum-VAs (also known as verapamil-sensitive VAs), (4) LV-other-VAs, and (5) RV-other-VAs. In this study, RVOT-VAs included VAs originating from the RVOT and pulmonary artery. LVOT-VAs were defined as VAs arising from the endocardium and epicardium of the LVOT and aortic sinus of Valsalva.

The prevalence, age at onset, sex characteristics, and results of the radiofrequency catheter ablation of idiopathic VAs are shown in Table 57.2. The prevalence of LVOT-

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TABLE 57.1 Prevalence, age at onset, gender characteristics, and results of the radiofrequency catheter ablation of idiopathic ventricular arrhythmias (VAs).

Arrhythmia origin	No. (%)	VT	PVC	Age	Male	Female	Male/Female	Success
(1) OT-VAs	480 (78)	156	334	52.8 ± 16.6	227	263	0.86	382 (78)
RVOT-VAs	331(53)	105	226	50.7 ± 16.1	135	196	0.68	290 (88)
LVOT-VAs	159 (25)	51	108	57.1 ± 16.8	92	67	1.37	92 (58)
(2) IT-VAs	80 (13)	27	53	61.6 ± 15.8	46	34	1.35	58 (73)
TA-FW-VAs	17 (3)	6	11	51.6 ± 18.4	11	6	1.85	14 (82)
IT-septum-VAs	34 (5)	9	25	65.9:13.5	16	18	0.89	17 (50)
MA-FW-VAs	29 (5)	12	17	62.4 ± 14.4	19	10	1.90	27 (93)
(3) LV-inferoseptum-VAs	27 (4)	27	0	39.3 ± 18.7	22	5	4.4	27 (100)
(4) LV-other-VAs	16 (3)	6	10	57.9 = 20.6	13	3	4.3	11 (69)
(5) RV-other-VAs	12 (2)	2	10	60.1 ± 9.4	7	5	1.4	8 (67)
Total	625 (100)	218	407	53.6 ± 17.1	315	310	1.01	486 (78)

FW, free wall; *IT*, inflow tract; *L(R)V*, left (right) ventricular; *L(R)VOT*, left (right) ventricular outflow tract; *MA*, mitral annulus; *PVC*, premature ventricular contraction; *TA*, tricuspid annulus; *VT*, ventricular tachycardia. LVOT-VAs were defined as VAs arising from the endocardium and epicardium of the LV outflow tract, and aortic sinus of Valsalva.
From Tanaka Y, Tada H, Ito S, Naito S, Higuchi K, Kumagai K, Hachiya H, Hirao K, Oshima S, Taniguchi K, Aonuma K, Isobe M. Gender and age differences in candidates for radiofrequency catheter ablation of idiopathic ventricular arrhythmias. Circ J 2011;75:1585–1591 With permission.

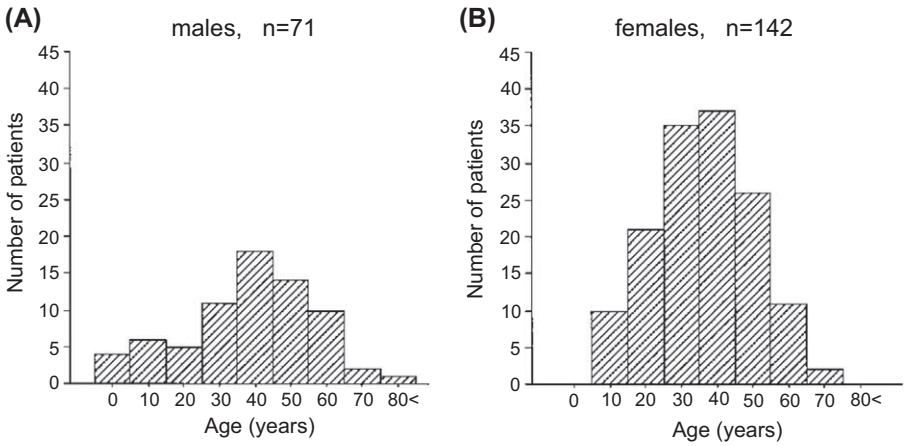

FIGURE 57.1 Age distribution among 213 patients with ventricular tachycardia originating from the right ventricular outflow tract. *From Nakagawa M, Takahashi N, Nobe S, Ichinose M, Ooie T, Yufu F, Shigematsu S, Hara M, Yonemochi H, Saikawa T. Gender differences in various types of idiopathic ventricular tachycardia. J Cardiovasc Electrophysiol 2002;13:633–8 With permission.*

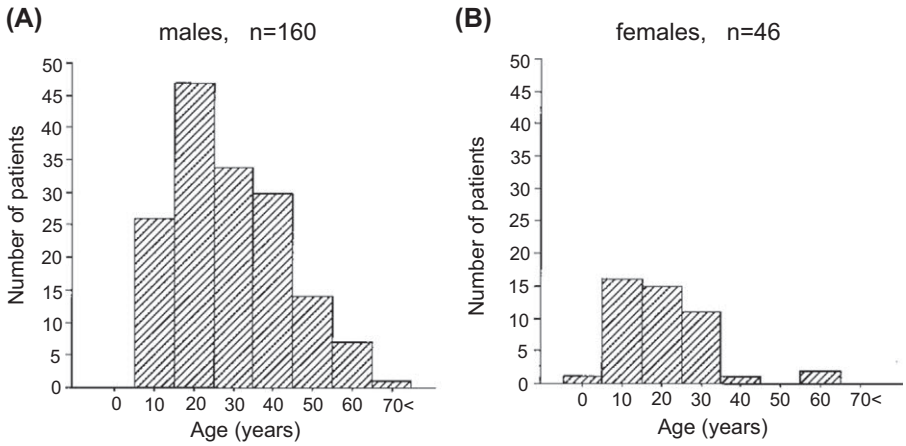

FIGURE 57.2 Age distribution among 206 patients with ventricular tachycardia originating from the left ventricle. *From Nakagawa M, Takahashi N, Nobe S, Ichinose M, Ooie T, Yufu F, Shigematsu S, Hara M, Yonemochi H, Saikawa T. Gender differences in various types of idiopathic ventricular tachycardia. J Cardiovasc Electrophysiol 2002;13:633–8 With permission.*

TABLE 57.2 Prevalence, age at onset, and gender characteristics of idiopathic ventricular arrhythmias (VAs).

Arrhythmia origin	No. (%)	VT	PVC	Age	Male	Female	Male/Female
(1) OT-VAs	490 (78)	156	334	52.8 ± 16.6	227	263	0.86
RVOT-VAs	331 (53)	105	226	50.7 ± 16.1	135	196	0.68
LVOT-VAs	159 (25)	51	108	57.1 ± 16.8	92	67	1.37
(2) IT-VAs	80 (13)	27	53	61.6 ± 15.8	46	34	1.35
TA-FW-VAs	17 (3)	6	11	51.6 ± 18.4	11	6	1.85
IT-septum-VAs	34 (5)	9	25	65.9 ± 13.5	16	18	0.89
MA-FW-VAs	29 (5)	12	17	62.4 ± 14.4	19	10	1.90
(3) LV-septum-VAs	27 (4)	27	0	39.3 ± 18.7	22	5	4.4
(4) LV-other-VAs	16 (3)	6	10	57.9 ± 20.6	13	3	4.3
(5) RV-other-VAs	12 (2)	2	10	60.1 ± 9.4	7	5	1.4
Total	625 (100)	218	407	53.6 ± 17.1	315	310	1.01

FW, free wall; *IT,* inflow tract; *L(R)V,* left (right) ventricular; *L(R)VOT,* left (right) ventricular outflow tract. *MA,* mitral annulus; *PVC,* premature ventricular contraction; *TA,* tricuspid annulus; *VT,* ventricular tachycardia. LVOT-VAs were defined as VAs arising from the endocardium and epicardium of the LV outflow tract and aortic sinus of Valsalva.

VAs increased with age compared to that in the RVOT-VAs, and the mean age of the patients with LVOT-VAs was higher than that of RVOT-VAs ($P < .0001$). In the IT-VAs, the mean age of the patients with MA-FW-VAs was higher than that of TA-FW-VAs ($P = .03$), and the tendency of the age distribution in the MA-FW-VAs and TA-FW-VAs was similar to that of the LVOT-VAs and RVOT-VAs, respectively. For both PVCs and VTs, there was a tendency that the right-sided VAs (RVOT-VA and TA-FW-VAs) occurred at a younger age than the left-sided VAs (LVOT-VAs and MA-FW-VAs). The LV septum-VAs were observed in younger patients.

The LVOT-VAs, TA-FW-VAs, MA-FW-VAs, LV septum-VAs, LV-other-VAs, and RV-other-VAs were more common in males than females, whereas the incidence of RVOT-VAs was 1.5 times more frequent in females than in males (male/female ratio, 0.68). The IT-septum-VAs were distributed almost equally between males and females. Although the number of patients with LV septum-VAs and LV-other-VAs was relatively small, those types of VAs were observed four times more often in males than in females. Fig. 57.1 shows the age distribution for the OT-VAs between males and females. There were two peaks of the onset of RVOT-VAs in both the male and female patients: the peaks were in the second and fifth decades of life in the female patients, and in the fifth and seventh decades in the male patients (Fig. 57.3A). The RVOT-VAs were more often observed in females in the second to third decade of life than in males. On the other hand, there seemed to be no sex difference in the age distribution between the male and female LVOT-VA patients (Fig. 57.3B). This study also shows that successful ablation

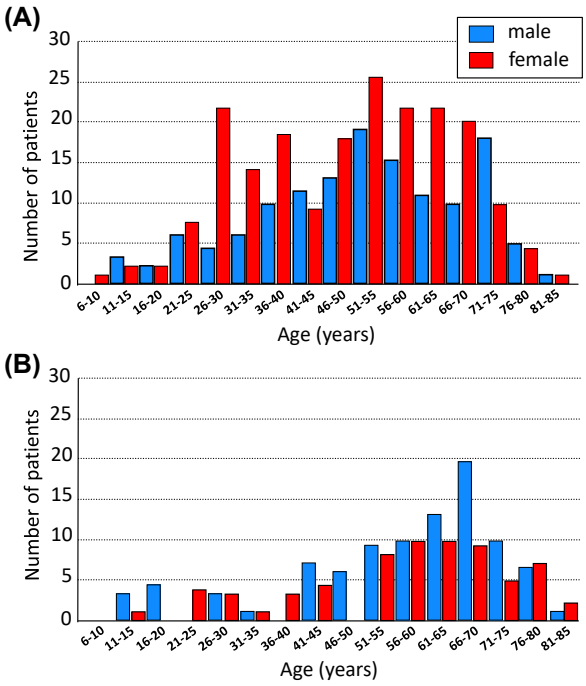

FIGURE 57.3 The distribution of the absolute number of male and female patients by age for the idiopathic ventricular arrhythmias (VAs) arising from the right (RVOT; A) and left (LVOT; B) ventricular outflow tracts. *From Tanaka Y, Tada H, Ito S, Naito S, Higuchi K, Kumagai K, Hachiya H, Hirao K, Oshima S, Taniguchi K, Aonuma K, Isobe M. Gender and age differences in candidates for radiofrequency catheter ablation of idiopathic ventricular arrhythmias. Circ J 2011;75:1585–91. With permission.*

rates, recurrence rates, and necessary repetitive operations were similar between males and females.

Sex differences in the idiopathic VAs with papillary muscle and ventricular crux origins

Recently, idiopathic VAs arising from papillary muscles and ventricular crux have been reported [6–10]. Papillary muscle VAs are found in 4%–12% of idiopathic VAs [3,6–8]. Those VAs originate more commonly from the LV posterior papillary muscle than from the anterior papillary muscle and could occur from RV papillary muscles. The mechanism is typically focal in nature and not reentrant. LV papillary muscle VAs were 1.5–2.0 times more frequent in men than in women, while the sex differences in the RV papillary muscle VAs has not been well established because of a paucity of available data [6–8]. Patients with LV papillary muscle VAs seem to be older than those with RVOT-VAs and LV septum-VAs, while those with RV papillary muscle VAs seem to be as old as those with RVOT-VAs.

VAs originating from the ventricular crux (Crux VAs) are found in 1.8% of idiopathic VAs and are classified into two type of VAs: apical and basal crux VAs [3,9,10]. These VAs appear to have a focal mechanism from the epicardium with programmed stimulation or burst pacing from the RV, and often require isoproterenol (catecholamine sensitive). Crux VAs seem to be distributed almost equally between males and females. The mean age of the patients with crux VAs is in their 50s, which seems to be older than that in those with RVOT-VAs.

Proposed mechanism of sex differences in the idiopathic VAs

RVOT-VAs are generally adrenergically mediated and sensitive to decreased intracellular calcium. The electrophysiologic and pharmacologic properties, which include sensitivity to adenosine, are similar for RVOT-VAs and LVOT-VAs, and cyclic AMP-mediated calcium-dependent delayed afterdepolarizations are considered as a common arrhythmogenic mechanism of those VAs [11]. However, some studies and case reports have suggested the possibility of reentry as an arrhythmogenic mechanism of LVOT-VTs, especially those with an epicardial origin that could be ablated from the aortic sinus cusp [12]. The increased prevalence of LVOT-VAs with age also suggests that increased myocardial fibrosis in the older population results in slower conduction. Therefore, the sex differences in idiopathic VTs may be related to different mechanisms and that LVOT-VTs may not merely represent a left-sided variant of RVOT-VTs. In fact, the VT mechanism in some LVOT-VTs and a considerable number of LV septum-VTs is considered to be a reentry [3,12], and those VTs are much less frequent in women than in men. A previous study demonstrated the relatively smaller transmural dispersion of repolarization across the ventricular wall, despite a longer total repolarization time, in females than males [13]. This may limit the reentry in females but may accelerate it in males.

Several mechanisms have been proposed to explain the sex differences in idiopathic VAs. One of those is associated with sex hormones [14]. The changes in the sex hormone levels, and sex differences in those levels, may be associated with the occurrences of VAs. Marchlinski et al. reported that the hormonal fluxes during premenstrual, gestational, and perimenopausal periods could be triggers for the initiation of RVOT-VTs [15]. Sex hormones could regulate the expression of cardiac ion channels. Progesterone increases the delayed rectifier K^+ current (Iks) through the nitric oxide production pathway and prevents cyclic adenosine monophosphate enhancement of the L-type Ca^{2+} current [16]. Philp et al. [17] showed that 17 β-estradiol could exert an antiarrhythmic effect by inhibiting Ca^{2+} channels, which indicates that the reduction in the 17 β-estradiol level may exert a proarrhythmic effect and could lead to the activation of Ca^{2+} channels. Hu et al. reported that, although the levels of testosterone and progesterone did not differ, the level of estradiol in male patients with idiopathic OT-VAs was significantly lower than that in the control males, which may result in activating Ca^{2+} channels and exert a proarrhythmic effect [18]. In this study, a significantly negative correlation was also found between the number of PVCs and the level of estradiol in idiopathic OT-VA male patients (Fig. 57.4). Further, they also reported that estrogen replacement therapy significantly reduced the PVC count in postmenopausal women with idiopathic OT-VAs [19]. Thus, OT-VAs may be

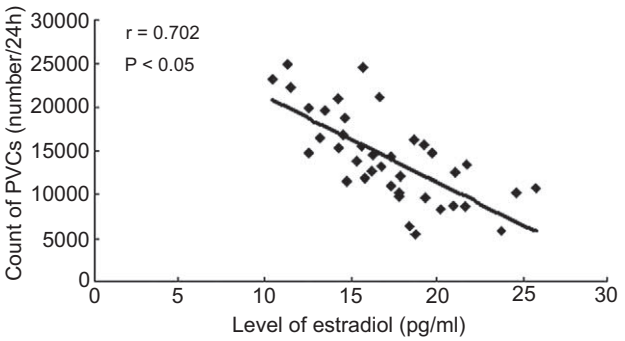

FIGURE 57.4 The relationship between the level of estradiol and count of premature ventricular contractions (PVCs) in adult male patients with idiopathic ventricular arrhythmias originating from the outflow tract. *From Hu X, Jiang H, Xu C, Zhou X, Cui B, Lu Z. Relationship between sex hormones and idiopathic outflow tract ventricular arrhythmias in adult male patients. Transl Res 2009;154:265–8 With permission.*

associated with the change in the Ca^{2+} channels mediated by estradiol. Tanaka et al. disclosed two peaks in the onset of RVOT-VAs in female patients [5], which might be partially due to sex hormonal effects. In the same study, LVOT-VAs had a male predominance. The patients with LVOT-VAs were older than those with RVOT-VAs. The patients with LVOT-VAs seem to be less affected by gonadal hormones than those with RVOT-VAs.

Other possible mechanisms are different distributions of ion channels between the sexes. James et al. reported sex-related differences in ventricular myocyte repolarization in the guinea pig [20]. They found in their study that IKs and the inward rectifier K^+ current differed between the sexes regardless of the menstrual cycle. Gaborit et al. further reported that male and female human hearts had significant differences in the ion-channel subunit composition, with female hearts showing a decreased expression of a number of repolarizing ion channels [21].

The autonomic nervous system could also play a role. As described before, RVOT-VTs tend to be catecholamine dependent. The autonomic tone may differ between males and females; a baseline sympathetic tone has been observed to be greater in middle-aged women than men [22]. Autonomic regulation, contributing to a different cardiac electrophysiology [23,24], might explain the sex differences in VAs. In a previous study [5], the prevalence of I-VAs with an origin in the LVOT increased with age as compared to that in the RVOT. The tendency of an age distribution was also observed in the patients with IT-VAs. However, the mechanism of this age distribution remains unknown. A previous study using a heart rate variability analysis demonstrated that the sympathetic tone increased with age [25]. The increasing sympathetic tone with age might cause a shift in the I-VA origin from the right side of the heart to the left side. However, no supporting data for this hypothesis were provided in this study.

Conclusions

Distinct sex differences are present in idiopathic VAs according to their site of origin. However, those have not been examined sufficiently or systematically especially for VAs with unusual origins. Previous studies do not reflect the real incidence and/or patient age at the first episode precisely. A further prospective study with a larger sample size, investigated at multiple centers and including patients with a younger age and those treated by medication only, is still needed to clarify the points described above.

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Chapter 58

Mapping and catheter ablation of idiopathic ventricular arrhythmias

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Introduction

Classification

Sustained ventricular arrhythmias (VAs) are most often related to myocardial structural heart disease such as healed myocardial infarction or cardiomyopathies. However, VA may also occur in patients with no apparent structural abnormalities. These arrhythmias called "Idiopathic Ventricular Arrhythmias" represent approximately 10% of all ventricular tachycardia (VT) diagnoses [1]. Idiopathic VA, similar to arrhythmias related to structural heart disease, may be classified according to the duration, morphology, mechanism, and anatomical origin of the arrhythmia. Based on duration, VAs are classified as (1) premature ventricular complex (PVC), defined as a premature single or double ventricular depolarization with or without mechanical contraction; (2) nonsustained VT (NSVT), defined as three or more sequential wide complex beats arising from the ventricles, with rate $\geq$100 bpm and terminating spontaneously in less than 30 s; and (3) sustained VT, when the tachycardia is continuous for >30 s or requires intervention for termination (Fig. 58.1). A further classification divides the arrhythmias according to the morphology as (1) monomorphic, if all the beats have a similar QRS morphology; (2) polymorphic, if there is a continuous beat-to-beat change in QRS morphology during the same tachycardia; and (3) multiple monomorphic VTs or multiple morphologies PVC, when morphologically different monomorphic VTs or PVCs from different locations are present. Idiopathic VAs are also divided into subtypes according to the site of origin identified by electrophysiological mapping and confirmed by successful catheter ablation. (1) Outflow tract VA include from the right ventricle (RV): right ventricular outflow tract (RVOT), pulmonary artery and para-Hisian; from the left side: left aortic sinuses of Valsalva, left ventricular outflow tract (LVOT) and LV summit, and between right and left deep intraseptal origin VA. Outflow tract VA are the most frequent site of origin and account for approximately two-thirds of idiopathic VA and 10% of all patients referred for VA ablation. Nonoutflow tract arrhythmias include (2) inflow tract VA from the peritricuspid and perimitral annular region (Fig. 58.2); (3) left ventricular fascicular VA (verapamil-sensitive), originating more from left posterior than anterior fascicle; and (4) intracavital arrhythmias originating from LV (with higher incidence of posteromedial than anterolateral papillary muscle) and RV papillary muscles and moderator bands (Fig. 58.3). In some anatomical locations, the site of origin is epicardial, more frequently occurring at the crux of the heart (epicardial area formed by the junction of the atrioventricular (AV) groove and posterior interventricular groove, approximately at the junction of coronary sinus (CS) and middle cardiac vein) and left ventricle (LV) summit (triangular region of the most superior part of the LV, bounded by left circumflex coronary artery, left anterior descending artery, and an approximate line from the first septal coronary artery laterally to the left AV groove) (Fig. 58.4).

Pathophysiology

The most frequent mechanism underlying idiopathic arrhythmias is focal triggered activity mediated by catecholamine-induced delayed afterdepolarizations, as a result of an increase in intracellular cyclic adenosine monophosphate (cAMP) after beta-adrenergic receptor stimulation and $I_{ca,L}$ activities. Idiopathic left fascicular VT (verapamil-sensitive) occurs primarily due to reentry involving both fascicle of left bundle branch and the Purkinje network.

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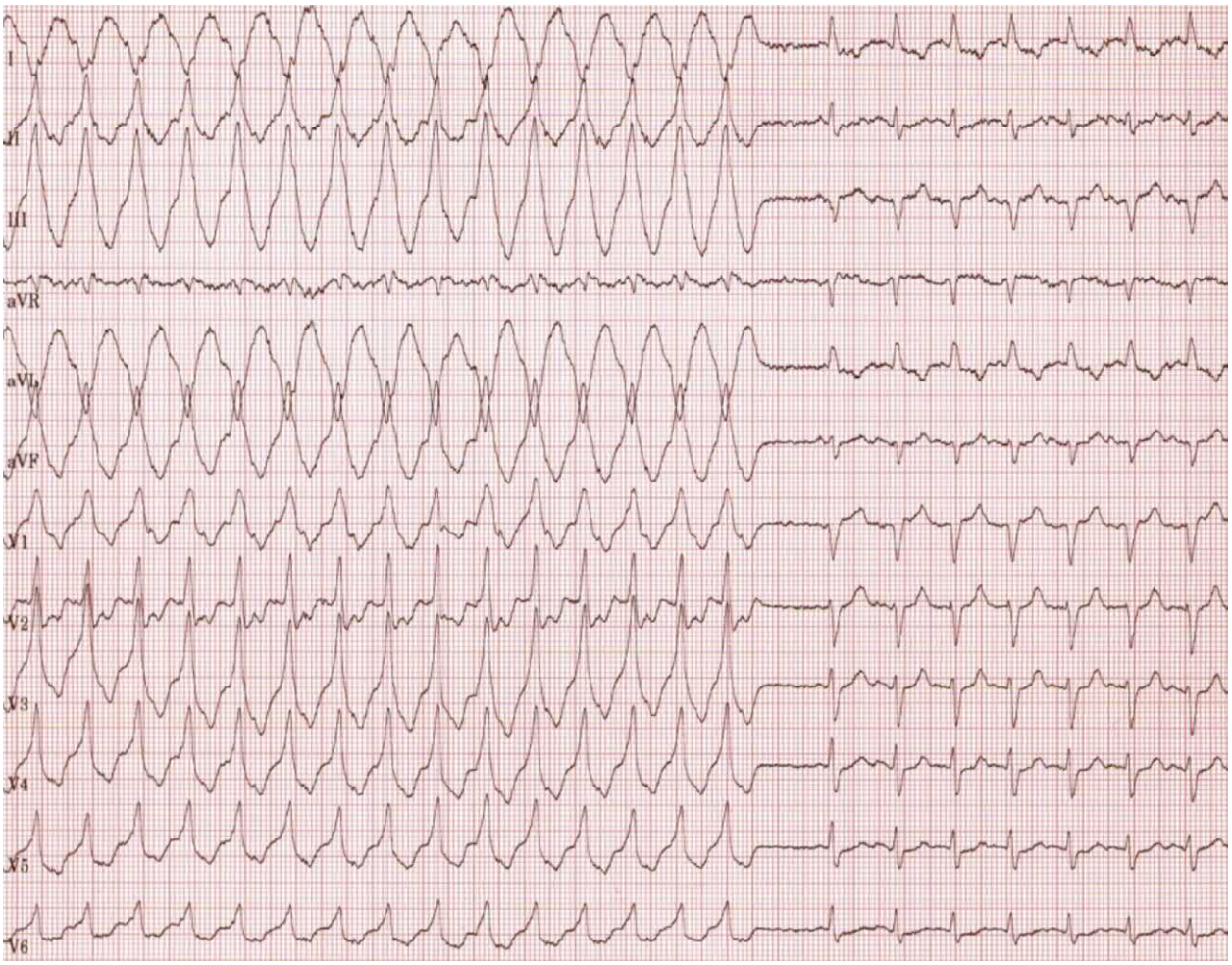

FIGURE 58.1 12-lead surface ECG of monomorphic idiopathic outflow tract ventricular tachycardia successfully ablated from the distal great cardiac vein epicardially.

Symptoms

Idiopathic VAs usually have a benign course and sudden death is rare, suggesting that these arrhythmias are rarely an early manifestation of occult cardiomyopathy. The arrhythmias can frequently be asymptomatic, especially when presenting as PVC or NSVT, and can be detected incidentally during routine examination. The symptoms can be due to post-PVC augmentation of contractility or post-PVC compensatory pause and include palpitations, fatigue, light-headedness, dyspnea, and chest discomfort. Presyncope and syncope can occur with increasing duration and rate of the VA. When the arrhythmia occurs as frequent PVC with a burden greater than 20%−24% and/or NSVT, it can cause reversible left ventricular dysfunction as a form of tachycardia-induced cardiomyopathy. In the absence of LV dysfunction, the therapy of idiopathic VT is largely guided by symptoms [1].

Sex differences in the incidence of idiopathic ventricular arrhythmias

Several studies analyzed the sex-dependent incidence of VAs. An early literature review of 748 patients with idiopathic VT included 387 (52%) female patients. RVOT-VT occurred twice more frequently in females (M/F ratio 0.49) and LVOT-VT occurred slightly more frequently in males (M/F ratio 1.38), whereas verapamil-sensitive intrafascicular LV-VT was three times more frequent in males (M/F ratio 3.37) [2].

A more recent study in the United States included between 2005 and 2013 614 patients with idiopathic VA. The incidence of idiopathic VT increased with age but was not different between sexes. In the symptomatic PVC group, the age-adjusted incidence was higher in females than in males (46.2 per 100,000 vs. 20.5 per 100,000) [3].

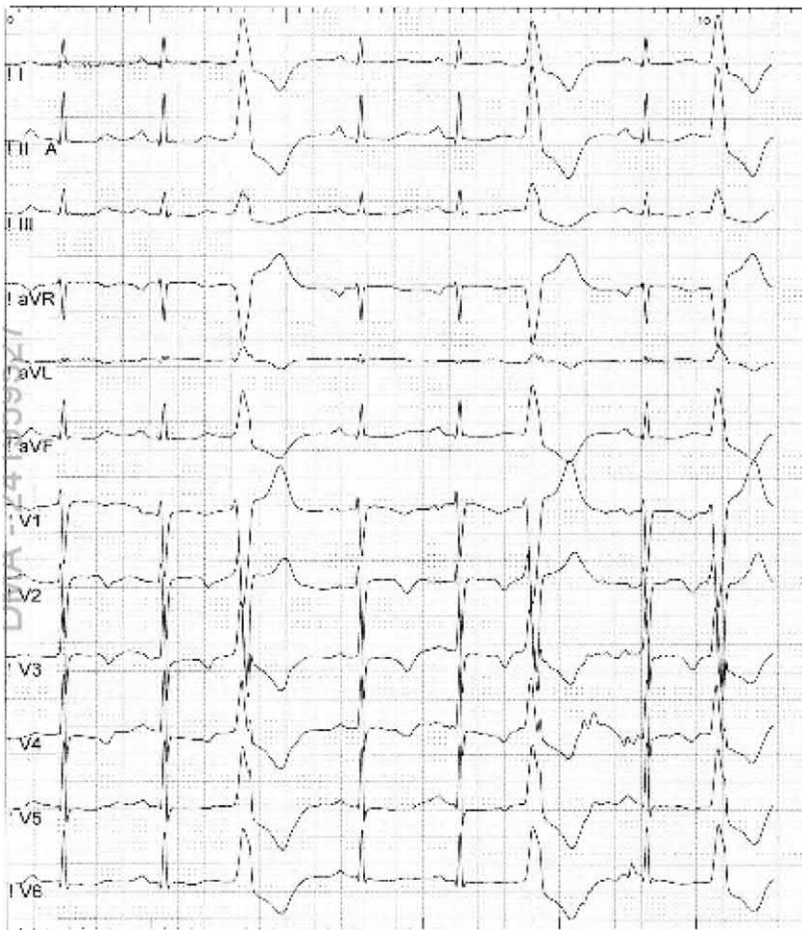

FIGURE 58.2 12-lead surface ECG of unifocal idiopathic premature ventricular complexes successfully ablated from the peritricuspid lateral wall of the right ventricle.

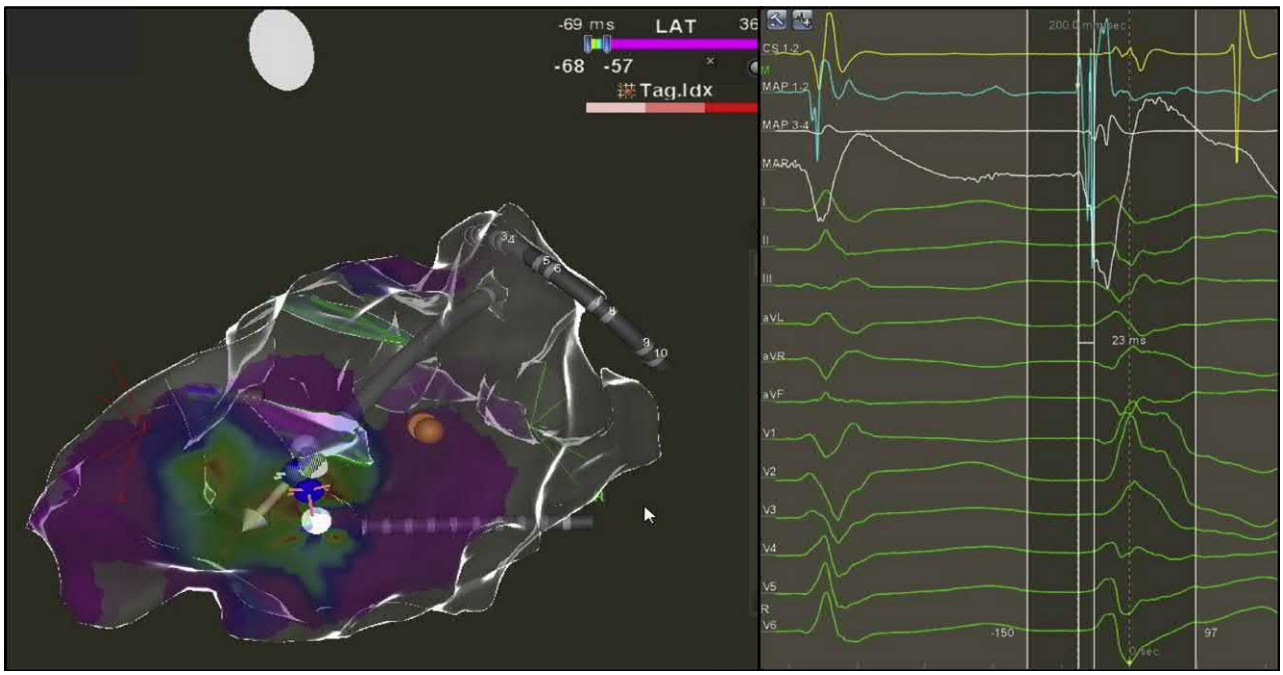

FIGURE 58.3 **3D electroanatomical activation map of a PVC successfully ablated from the left anterior papillary muscle.** On the left side, electroanatomical reconstruction of the left ventricular shell with projected color coded activation mapping with a gradient from red (earliest activated site) to purple (latest activated site). On the right side, surface ECG and intracardiac EGM recordings during sinus rhythm (first beat) and PVC (second beat) show the earliest signal in the left anteromedial papillary muscle 23 ms before the onset of QRS complex. From top to below are shown intracardiac coronary sinus distal bipolar (CS 1−2) EGM, intracardiac ablation distal and proximal bipolar (Map 1−2, Map 3−4), and distal unipolar (Map 1) EGMs and surface ECG leads I, II, III, aVL, aVR, aVF, and V1−V6.

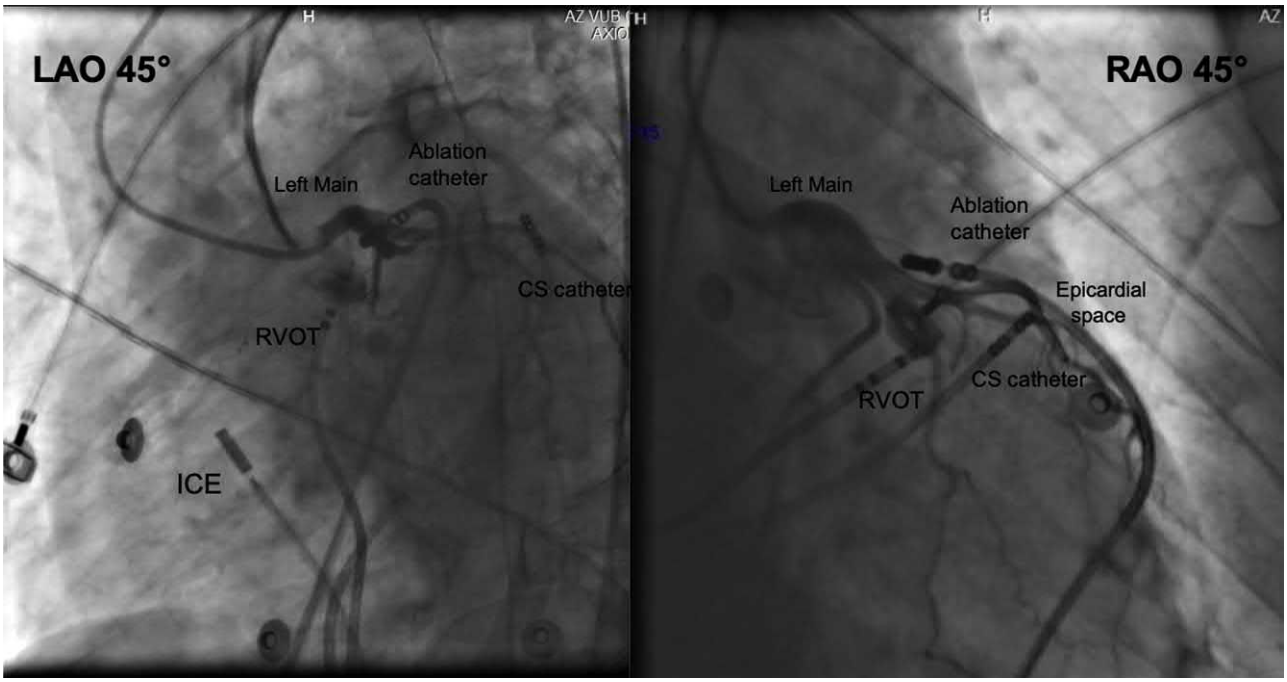

FIGURE 58.4 Coronary angiography during epicardial mapping of a PVC from the LV summit following failed endocardial ablation attempts from the right and linker ventricular outflow tract. Percutaneous epicardial mapping at redo ablation of PVC after unsuccessful ablation from the RVOT and LVOT. On the left side left anterior oblique (LAO) 45 degrees and on the right side right anterior oblique (RAO) 45 degrees views are shown. The intracardiac echocardiography (ICE) probe is positioned in the right atrium and two quadripolar catheters in the RVOT and coronary sinus (CS). The ablation catheter is positioned in the LV summit at the earliest site of local activation during PVC. The coronary angiography shows the close proximity between the ablation catheter positioned on the target site and left anterior descending coronary artery. Ablation could not be performed at this target site due to the high risk of coronary artery injury.

In another smaller study of 152 patients undergoing focal idiopathic VA ablation procedures, male sex was the only independent predictor of PVC-mediated cardiomyopathy in both univariate and multivariate analyses [4].

Pathogenic mechanisms for sex-based differences in incidence

Although the pathophysiologic basis for sex-based differences in the incidence of idiopathic VA remains unknown, some mechanisms are proposed to explain the variability. The role of sex-specific triggers was described in a small report of 47 patients with RVOT-VT. 20 (59%) of 34 female patients reported RVOT-VT initiation with recognized states of hormonal flux (premenstrual, gestational, perimenopausal, and coincident with the administration of birth control pills), whereas in men arrhythmias were more commonly initiated with exercise and/or stress [4]. The role of sex hormones in VAs was confirmed in an animal study, in which acute administration of 17 beta-estradiol in dogs could prolong ventricular repolarization and accentuate the occurrence of early afterdepolarization and Torsade de pointes events. Experimental models showed differences ion-channel activity (particularly I_{ks} and inward rectifier K^+ channels) and ion-channel subunit composition resulting in longer action potential duration and longer cardiac repolarization times in females [5]. Smaller transmural dispersion of refractoriness across the ventricular wall [6], longer Purkinje-cell APD [7], and faster His−Purkinje conduction [8] was described in females, which may also explain the greater incidence of LV reentrant arrhythmias in men.

Another potential mechanism for the observed sex differences in incidence of VA is the difference in autonomic tone between males and females. In middle-aged women, higher baseline sympathetic tone was reported than in men. This finding may explain the higher incidence of RVOT-VT in middle-aged women, given the catecholamine-dependent mechanism underlying these arrhythmias [9].

Sex-associated variability in the incidence of idiopathic VA may be also explained by differences in symptoms perception and greater inclination to seek medical attention in women. Some studies reported greater risk to develop tachycardia-induced cardiomyopathy in males, perhaps due to later referral to medical attention [10,11].

In summary, several factors may play a role in the observed sex-based differences in the incidence and pathomechanism of idiopathic VA. Further clinical and experimental studies are needed to clarify the relative contribution of each of these factors.

Mapping and catheter ablation of idiopathic ventricular arrhythmias

Indication for mapping and catheter ablation

Catheter ablation of idiopathic VAs is an effective therapy, with reasonably high acute and long-term success rate and low incidence of procedure-related complications. The 2019 Expert Consensus Statement on Catheter Ablation of Ventricular Arrhythmias recommends catheter ablation in patients with frequent and symptomatic idiopathic PVCs originating from RVOT in preference to metoprolol and propafenone (Class I). Similarly, catheter ablation is Class I recommendation for patients with RVOT-VA, idiopathic monomorphic sustained VT, symptomatic VAs from right and LV at sites other than the outflow tracts, and idiopathic left fascicular reentrant VT or focal fascicular VT when antiarrhythmic medications are ineffective, not tolerated, or not preferred. Catheter ablation is useful if medications are ineffective or not tolerated for patients with symptomatic idiopathic VA from endocardial and epicardial LVOT, from epicardial coronary venous system, from para-Hisian sites and from posterior−superior process of LV (Class IIa). In patients with a suspected PVC-induced cardiomyopathy, catheter ablation can be considered as an alternative to long-term antiarrhythmic drug therapy, particularly in patients with monomorphic PVCs, or PVCs of an RVOT origin (Class I) [1]. The major complications associated with catheter ablation are related to vascular access (femoral pseudoaneurysm and arteriovenous fistula), myocardial perforation with tamponade and hemopericardium, thromboembolic events (more frequent in the left-side ablation), conduction system damage (AV block and left bundle branch block resulting in heart failure), pericarditis, RV lead dysfunction, and cardiopulmonary resuscitation during the procedure [12].

Technique for mapping and catheter ablation

Catheter ablation of idiopathic VA is mostly based on activation and pacemapping. Activation mapping is performed by recording local unipolar and bipolar electrograms from multiple sites during VA. In focal VA, the site of origin, showing earliest local bipolar electrogram preceding the QRS complex with QS configuration of the unipolar signal, represents the target for ablation. The activation map shows a centrifugal spread of propagation from the site of origin (Fig. 58.5). Pacemapping is a technique used to locate the origin of a PVC or VT by stimulating the myocardium to reproduce the clinical 12-lead ECG morphology. The optimal site should match the QRS morphology of the clinical arrhythmia. Comparison of the 12-lead ECG is usually expressed with a scale from 0 to 12, but recently computer-assisted comparison may help to quantify this correlation in different mapping systems. Activation mapping is more accurate, as a similar paced QRS morphology may be seen over a relatively large area, but pacemapping can be helpful when the VA is infrequent.

Entrainment is a helpful maneuver in reentrant VAs, such as the verapamil-sensitive VAs. This maneuver is based on resetting the tachycardia during pacing at different sites that are inside or outside of the reentry circuit. The analysis of the QRS morphology during pacing and of the postpacing interval after cessation of pacing provides information about location of the reentry circuit. Entrainment requires sustained and stable tachycardia without any modification or interruption during pacing.

The recent consensus statement on Catheter Ablation of Ventricular Arrhythmias suggests that electroanatomic mapping (EAM) can be useful in patients with idiopathic VA (Class IIa). The EAM systems reconstruct the cardiac chamber combining cardiac electrical information obtained from catheter-mounted electrodes and three-dimensional spatial location information. Several EAM systems are commonly used in clinical practice. The CARTO mapping system (Biosense-Webster, Diamond Bar, CA) uses a magnetic-based technology to localize the catheter and target the recorded electrograms. This system also provides the possibility to use the intracardiac ultrasound catheter to reconstruct the cardiac chamber geometry. The EnSite Precision system (Abbott Laboratories, Abbott Park, IL) uses a voltage and impedance-based technology to localize diagnostic and ablation catheters. The Rhythmia HDx mapping system (Boston Scientific, Marlborough, MA) uses both magnetic- and impedance-based methods. EAM allows the operator to reduce procedural fluoroscopy time and to annotate and revisit regions of interest. Maps created using these systems are influenced by accurate electrograms annotation, catheter contact with tissue, type of rhythm mapped, direction of activation wavefront propagation, and size and spacing of mapping electrodes. Multielectrode mapping catheters are developed to allow simultaneous and fast acquiring of multiple electrical information from different sites during the same beat. With smaller electrode size and interelectrode spacing, multielectrode mapping catheters allow to create high-resolution and high-density EAM, facilitating the identification of site of VA origin.

Technique for catheter ablation

Ablation success requires creation of adequate and durable lesions. The most used energy for ablation is unipolar radiofrequency energy (Fig. 58.6). Conventional unipolar radiofrequency catheter ablation delivers current between the catheter tip and a dispersive skin patch. Depth and the size of the lesions are limited by the amount of energy that can be safely delivered to the tissue. Too much power will result in overheating of the tissue with consequent thrombus formation or steam pop creation with tissue disruption. Irrigation of the ablation tip reduces tissue

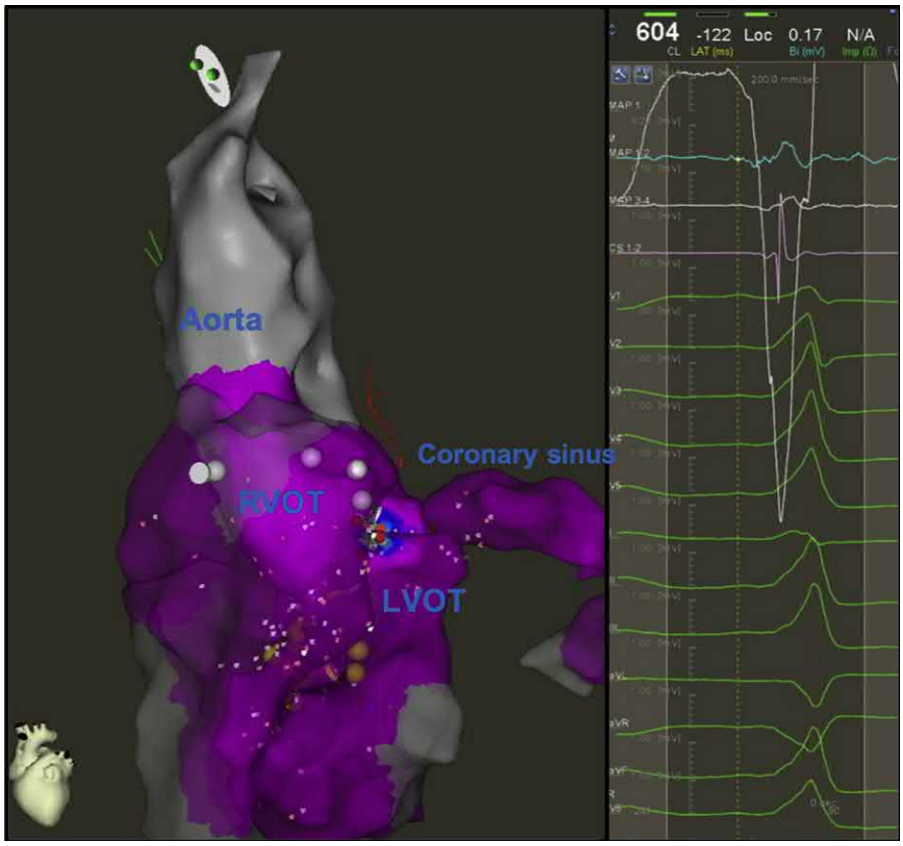

FIGURE 58.5 3D electroanatomical activation map of a PVC successfully ablated from the left coronary cusp. On the left side, reconstruction of the left and right outflow tracts, aortic cusps, and coronary sinus with activation map showing the earliest local activation (red color zone). *Yellow dots* show regions with His potential recording; *red dots* show the successful ablation site; *gray dots* show the pulmonary valve position. On the right side, surface ECG and intracardiac EGM recordings depict the earliest signal in the left coronary cusp, with presystolic fractionated bipolar signal during PVC. From top to below are shown intracardiac ablation distal unipolar (Map 1) and bipolar (Map 1−2) EGMs, coronary sinus (CS 1−2), EGM recorded at the earliest activation site in the great cardiac vein, and surface ECG leads I, II, III, aVL, aVR, aVF, and V1−V6.

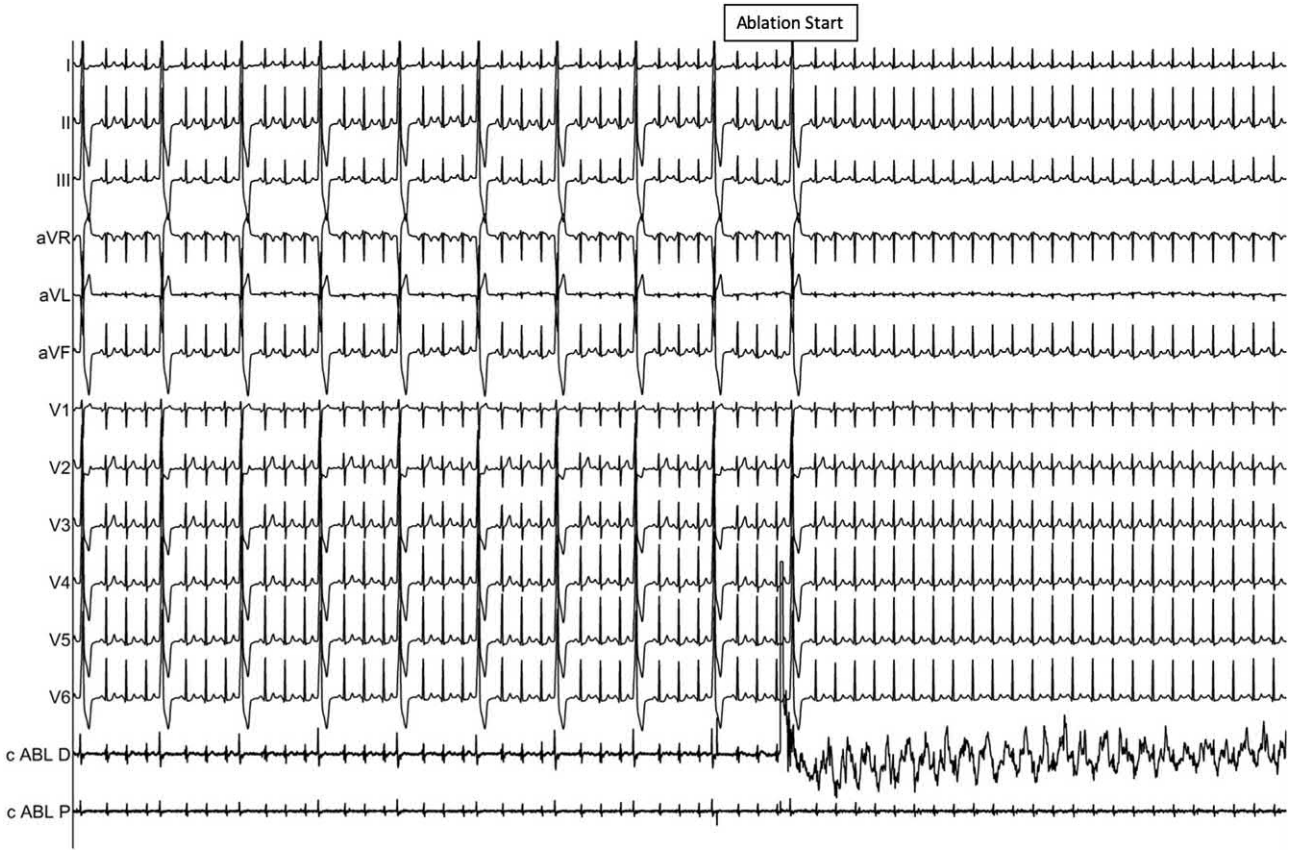

FIGURE 58.6 Successful ablation of PVC in the left ventricular outflow tract. 12-lead ECG and intracardiac ablation catheter distal (Abl D) and proximal (Abl prox) bipolar EGMs continuous recording before and during initiation of radiofrequency ablation at the site with earliest local activation (paper speed 6 mm/s). After initiation of RF energy delivery, the previously frequent unifocal outflow tract PVCs disappear.

interface temperature allowing larger and deeper lesions with less risk of thrombus and steam pops. Monitoring of impedance drop during ablation is an important parameter to assess the lesion formation and to avoid steam pops.

An important determinant of the lesion size is the contact between the catheter and the tissue. In the last decade, ablation catheters with contact-force sensor have become an integral part of RF catheter ablation. In the ventricle, RF applications with contact force >10 g are more likely to result in electrical inexcitability. Contact-force measurement may also help to avoid complications by extensive pressure.

Recently, for deeper arrhythmogenic substrate, new techniques have been developed. Hypotonic saline fluid (0.45% NaCl) is a less conductive irrigant that allows delivering greater energy to the tissue, but with a higher risk of steam pops [13].

Simultaneous unipolar or bipolar RF delivery may create larger lesions than sequential ablations at each of these sites. It delivers energy between two electrodes placed on opposite side of a target site [14].

Infusion needle ablation is a technique used to reach intramural arrhythmogenic focus. An extendable/retractable needle at the tip can function as an intramural electrode for temperature-controlled delivery of RF energy during saline irrigation [15].

Transvascular ethanol ablation is performed injecting alcohol retrogradely into the coronary venous system, with lower risk of coronary artery injuries. It allows the creation of controlled infarction with great ventricular ablation lesions [16].

Cryoablation is rarely used for VAs ablation due to smaller lesion size and higher recurrence rate. It may be helpful in ablation of para-Hisian VA for lower risk of permanent AV block. The better stability due to tissue adherence of the tip during ablation may provide additional utility for the VAs coming from highly mobile papillary muscles.

General approach for catheter ablation of idiopathic ventricular arrhythmias

For focal VAs, activation mapping is the most accurate technique to identify the site of origin. Presence of spontaneous and monomorphic ventricular beats is needed to perform an accurate map. For this purpose, all the medication should be discontinued for at least five half-lives before the procedure. Sedation with long-acting medication can decrease the number of spontaneous beats and the inducibility of VAs. Administration of catecholaminergic medication or limited physical activities such as hand grip or leg-raising exercise may elicit the arrhythmia.

The most frequent site of origin for idiopathic VA remains the RVOT. For VAs with left bundle branch block morphology, mapping should start at the RVOT and PA. When catheter ablation from the RVOT endocardium and pulmonary artery failed, a stepwise should be performed to map the adjacent structures. Mapping the great cardiac vein, anterior interventricular vein, and its septal branches via the CS provides useful information prior to left heart catheterization (Fig. 58.7). If mapping indicates a focus outside these structures, mapping of the sinuses of Valsalva and endocardial LVOT should be attempted via retroaortic approach (Fig. 58.8). When the ablation is not successful from the endocardium and CS, percutaneous access of the pericardial space permits to map and ablate on the epicardial surface.

Ablation of VA originating from the papillary muscles can be challenging due to multiple morphologies and difficulties to achieve and maintain sufficient contact during ablation. VAs originating from LV papillary muscles are more frequent than that from RV papillary muscles. In the LV, the arrhythmia is more frequently coming from posteromedial than anterolateral papillary muscle (Fig. 58.9). In these arrhythmias, pacemapping is less accurate than in other focal arrhythmias. Cryoablation can be a useful option improving catheter stability during lesion delivery [17].

Detailed knowledge of anatomy can help to understand the relation between adjacent structures and improve success rates of the procedure. Preprocedure CT and magnetic resonance imaging (MRI) can be registered and merged with EAM in some mapping systems. ICE can be helpful to determine catheter ablation tip location in relation to valve, coronary artery, papillary muscles, and moderator band.

Verapamil-sensitive fascicular reentrant VT is the most common form of idiopathic left-sided VT. It was initially described as an arrhythmia induced by atrial pacing and characterized by right bundle branch block and left-axis configuration in patients without structural heart disease. During tachycardia, two typical groups of Purkinje potentials (P1 and P2) may be recorded from a mapping catheter placed along the midseptum. P1 are a middiastolic potential with proximal to distal activation along the septum, while P2 are fused presystolic Purkinje potentials with distal to proximal activation. In sinus rhythm, P2 potentials come later than the His potential and before the QRS onset, representing the activation of the left posterior fascicle. During tachycardia, P1 potentials represent the anterograde activation of the tissue with decremental and verapamil-sensitive properties; P2 potentials represent the activation of the left posterior fascicle or Purkinje fibers close to it and are not part of the circuit. The retrograde limb of the circuit is likely to be the left ventricular septal muscle. In the left posterior fascicular VT, the ablation target is the apical third of the septum with diastolic Purkinje potential (P1), without risk to induce LBBB or AV block. When the

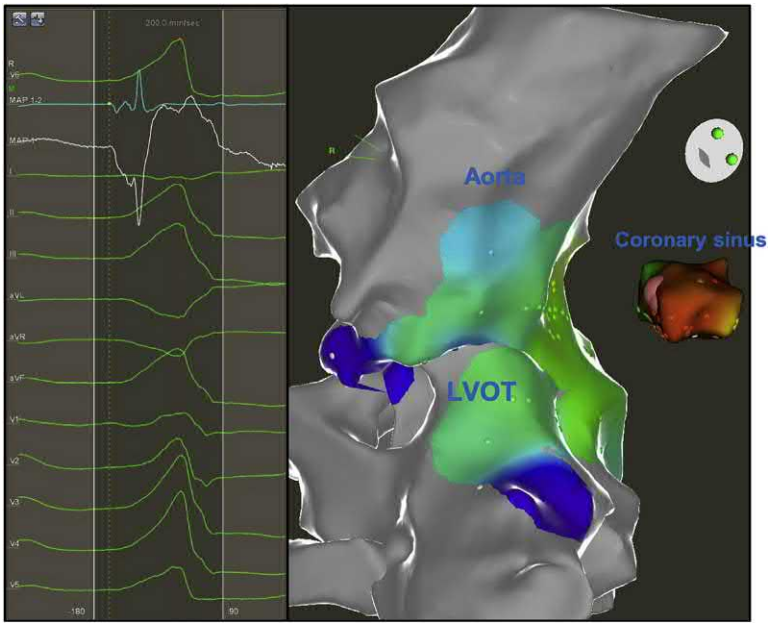

FIGURE 58.7 3D electroanatomical activation map of a PVC successfully ablated from the great cardiac vein. On the left panel surface ECG and intracardiac EGM recording depict the earliest signal during PVC. From top to below are shown V6, intracardiac ablation distal bipolar (Map 1−2) and unipolar (Map 1) EGMs, surface ECG leads I, II, III, aVL, aVR, aVF, and V1−V5. On the right side electroanatomical reconstructions of the left outflow tract, aortic cusps, and great cardiac vein anatomical shell and color coded activation mapping with a gradient of color from red (earliest activated site) to purple (latest activated site). *Red dots* show the successful ablation site.

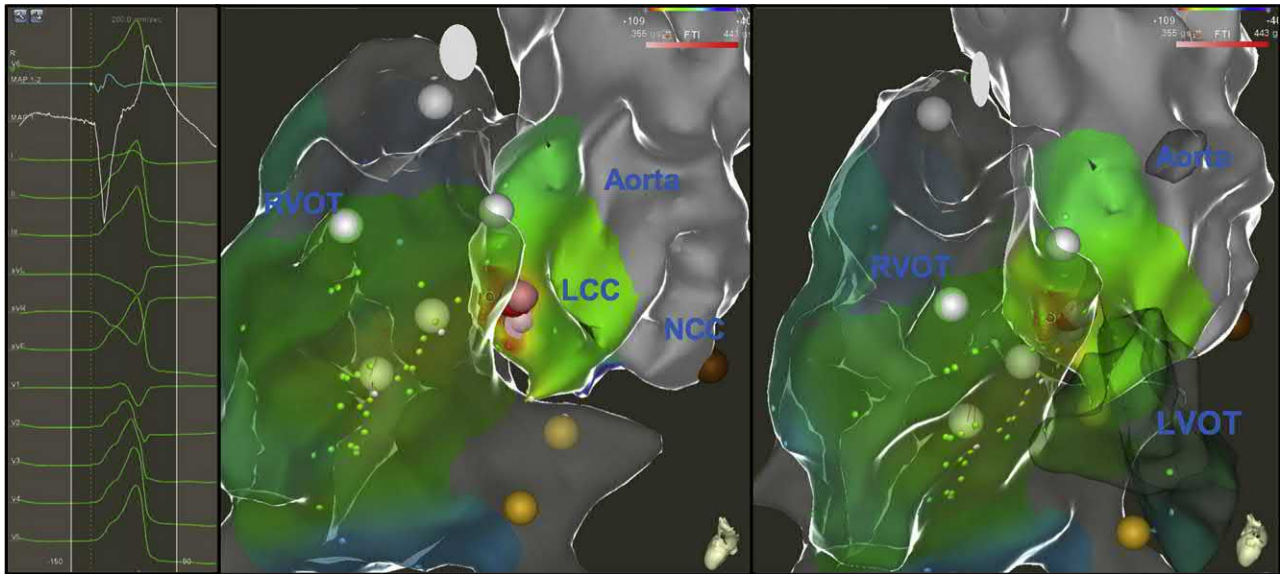

FIGURE 58.8 3D electroanatomical activation map of a PVC successfully ablated from the intercommissural region between the right and left coronary cusp. On the left side of the panel surface ECG and intracardiac EGM recordings show the earliest ventricular activation signal during PVC. From top to below are shown V6, intracardiac ablation distal bipolar (Map 1−2) and unipolar (Map 1) EGM recordings, and surface ECG leads I, II, III, aVL, aVR, aVF, and V1−V5. On the middle and right side panel electroanatomical reconstructions of the left outflow tract, aortic cusps, and RVOT with local activation times shown with color gradient from red (earliest activated site) to purple (latest activated site) projected on the anatomical shell. *Yellow dots* show regions with His potential recording, *red dot* the successful ablation site, *gray dots* the pulmonary valve position, and brown dot show the noncoronary cusp position (NCC).

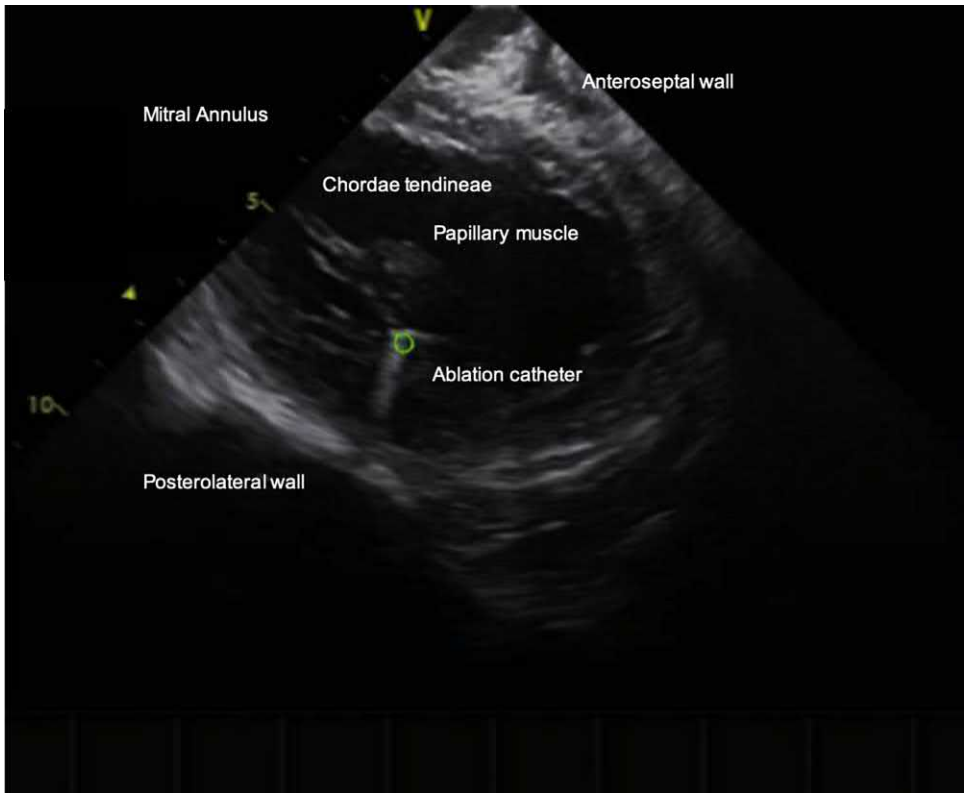

FIGURE 58.9 Intracardiac echocardiography (ICE)–guided mapping and site of successful ablation of a PVC originating from the posteromedial papillary muscle. 2D-intracardiac echocardiography image of the left ventricle and posteromedial papillary muscle showing the position and contact of the ablation catheter tip (*green circle*) with the papillary muscle at the site where earliest activation during PVC was recorded and successful ablation was performed.

tachycardia is not inducible, or the P1 and P2 potentials cannot be recorded, an empirical anatomical approach may be useful. First, during sinus rhythm, the VT exit site is identified by pacemapping and energy is delivered to this site. Subsequently, an empirical linear ablation lesion is performed at midseptum, perpendicular to the long axis to LV, 10–15 mm proximal to the VT exit. The circuit of the left anterior fascicular tachycardia is a mirror image of the left posterior. Upper septal fascicular VT has a narrow QRS with inferior frontal plane axis. P1 represents the activation of Purkinje fibers at the left ventricular septum, while P2 potentials can be recorded along the left anterior and posterior fascicles. Both fascicles represent the anterograde limb of the reentrant circuit. The left ventricular midseptum is usually an effective target for ablation of these arrhythmias [18,19].

Sex differences in mapping and catheter ablation of idiopathic VA

Unlike atrial fibrillation and VAs associated with structural heart disease, in most studies of catheter ablation of all idiopathic VA, female and male patients are equally represented (42%–71%). In reports of catheter ablation of left papillary muscle-VA, slightly lower number of female (mean: 37%) than male patients are enrolled. In contrast, in studies of catheter ablation of fascicular VT, female patients are underrepresented (mean: 22%), according to the lower incidence of this arrhythmia in women. In most studies, sex-based differences in outcome and complication rates were not reported. Recently, few studies focused on evaluation of sex-related differences in outcome and complication of catheter ablation of idiopathic VA.

A small retrospective study in Taiwan analyzed sex differences in the electroanatomic voltage mapping of the RV. 93 (67% female) patients were enrolled with the diagnosis of idiopathic RVOT-VT [20]. Structural heart disease (including arrhythmogenic right ventricular cardiomyopathy according to 2010 Task-Force criteria) was excluded by transthoracic echocardiography and cardiac catheterization [21]. Repolarization abnormalities (T-wave inversion in right precordial leads from V1 to V3) were noted in 10% of male versus 19% of female patients. Echocardiography showed in 21% and 13.8% of males RV

dysfunction and RV regional dyskinesia, respectively, compared to 19% and 20.6% of female patients ($P = NS$). Areas with a bipolar electrogram voltage <0.5 mV were identified as scar zones, whereas areas with bipolar voltage between 0.5 and 1.5 mV as low voltage zones. Male patients had higher mean RV bipolar voltage than females (3.7 ± 0.9 mV vs. 3.0 ± 0.7 mV, $P = .03$). There was no statistical difference in the percentage of scar zone distribution between males and females. However, more females had low voltage zone in the RVOT free wall as compared with males (27% vs. 6.7%, $P = .02$). Catheter ablation was performed with similar acute success and VT recurrence rates in the two groups (73.9 vs. 65.5% and 26.1 vs. 27.6%; $P = .47$ and .89, respectively). The authors explained the findings of lower right ventricular bipolar voltage and more low voltage zones in the RVOT free wall in women as a result of remodeling, rather than the cause of VT. This study has several limitations. First, some patients had RV regional abnormalities, repolarization abnormalities in precordial V1−V3 leads, and sometimes polymorphic VT suggesting the presence of subclinical structural right ventricular disease [22]. Additionally, no cardiac MRI was performed. A similar study of patients presenting with presumed idiopathic VT of left bundle branch block and inferior axis morphology reported that 25% of patients had areas of RV scar, as determined by low voltage in electroanatomic maps and fibrosis in endomyocardial biopsies, confirming that an early/minor form of ARVC/D may mimic idiopathic RVOT tachycardia [23]. Furthermore, the bipolar electrogram amplitudes depend on electrode size and spacing, orientation of the catheter, wavefront propagation, and contact between mapping catheter and tissue. The electroanatomic maps were done in the era of non−contact-force sensing catheters. Areas of low voltage may be due to suboptimal contact of the ablation catheter in the RVOT free wall. Due to the limitations of this study and the scarcity of data in the literature, further studies are needed to characterize sex-based differences in substrate of idiopathic VA.

In a large single center retrospective study of 625 consecutive patients undergoing catheter ablation of symptomatic and drug-resistant idiopathic PVC, NSVT and VT 310 females (50%) were included [24]. The large majority (78%) of arrhythmias originated in the outflow tracts (specifically 53% in the RVOT and 25% in LVOT) and 13% of arrhythmias from the septal, peritricuspid, or perimitral free wall regions, 4% from the LV fascicles, 3% from other region in the LV, and 2% from other structure in the RV. Similar to other previous studies, RVOT arrhythmias were 1.5 times more frequent in women than in men (male/female ratio 0.68), while LVOT, mitral, and tricuspid annular arrhythmias were slightly (1.37, 1.90, and 1.85 male/female ratio, respectively) and fascicular arrhythmias significantly more (4.4 male/female ratio) frequent in men. Nonoutflow tract LV and RV arrhythmias (papillary muscles, moderator band, and epicardial origin) were also more frequent in men (4.3 and 1.4 male/female ratio, respectively). The ablation success in this study varied between 58% and 100% and was dependent on the region of origin. Ablation success was significantly higher in RVOT-VA than in LVOT-VA (88% vs. 58%). The success rate in septal origin of VA was significant less than in mitral and tricuspid annular VA (50% vs. 89%). The success of ablation was not different between females and males, and in multivariate analysis, female sex was not an independent predictor of outcome.

Similar results were reported in another smaller single center study of 114 consecutive patients including 55 (48%) females without structural heart disease undergoing catheter ablation for monomorphic VT [25]. Women younger than 31 years of age had a higher incidence of idiopathic VA (67%) than VA related to structural heart disease. The baseline characteristics (age, left ventricular ejection fraction, body mass index, implanted cardiac defibrillator) were not different between male and females. There were no sex-related differences in the procedural data characteristics (radiofrequency time per procedure, epicardial ablation, and noninducibility after last procedure). The complication rate of the ablation procedure in females was 7.1%. Pericardial effusion/tamponade occurred in 3.1% of female patients, as frequently as in men. The VT recurrence free survival at 1 year was 87% in men and 76% in women with no statistical difference between males and females ($P = .546$). The mortality rate was 0% for men and 1.8% for women ($P = NS$). In this study, the percentage of patients who failed amiodarone therapy and underwent catheter ablation as first-line therapy or as repeated procedure was the same in both groups. These data are in contrast to study results of catheter ablation of atrial fibrillation. In atrial fibrillation, females are referred for ablation later than men, after a longer duration of symptoms, and after failure of more antiarrhythmic drugs [26].

In summary, all of the studies up to date reported that catheter ablation of idiopathic VAs is equally effective with the same risk of complications in both sex groups (Table 58.1).

TABLE 58.1 Registries of catheter ablation of idiopathic ventricular arrhythmias focused on sex differences.

Study	Enrollment population	Therapy	Total enrollment	Women %	Outcome
Tanaka et al. [24]	Monomorphic idiopathic VA (VT and PVC)	3DEAM-guided nonirrigated tip, no contact-force sensor	625	49.6%	Total success rate 78%, depending of origin of VA. Female sex is not correlated with success ($P = .85$)
Baldinger et al. [25]	Sustained monomorphic VT	3DEAM-guided irrigated tip, contact-force sensor	114	48%	Estimated recurrence free survival at 1 year: 87 ± 5% M vs. 76 ± 6% W ($P = .546$) Mortality rate: 0% M versus 1.8% W Similar complication rate
Liao et al. [20]	RVOT-VT	3DEAM-guided non–contact-force catheter	93	79.4%	Acute success: 73.9% M vs. 65.5% W ($P = .47$) VT recurrence: 26.1% M vs. 27.6% W ($P = .89$)

3DEAM, 3D electroanatomic map; *M*, male; *PVC*, premature ventricular complex; *RVOT*, right ventricle outflow tract; *VA*, ventricular arrhythmias; *VT*, ventricular tachycardia; *W*, women.

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Part XIV

Electrophysiology in pregnancy

Chapter 59

Hormone and autonomic changes of pregnancy and their impact on cardiac electrophysiology

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Introduction

During pregnancy, there are several physiologic changes that are regulated through hormonal, hemodynamic, and autonomic alterations. It is common for women during pregnancy to experience some form of palpitations, fortunately the majority of which are benign. A large retrospective study showed that 0.17% of hospital admissions during pregnancy are related to arrhythmias including supraventricular tachycardia (SVT), atrial fibrillation, ventricular tachycardia (VT) or fibrillation, and atrioventricular (AV) block [1]. The literature is not clear as to whether new onset arrhythmias such as SVT are more likely during pregnancy, but an increase in episodes in women with preexistent arrhythmias is more common. However, a woman with asymptomatic Wolff−Parkinson−White syndrome may experience her first episode of SVT during pregnancy [2,3]. In this chapter, we will explore the hormonal and autonomic electrophysiologic effects of pregnancy, which can lead to cardiac arrhythmias.

Hormonal effects of pregnancy and relation to arrhythmia

Normal pregnancy is associated with a cascade of hormonal changes throughout pregnancy and delivery including a rise in human chorionic gonadotropin postovulation peaking at 60−90 days after gestation, a rise in progesterone during the first trimester, increase in estrogen levels toward the end of the first trimester, increased relaxin later in pregnancy up to 10 times the prepregnant levels, an increased sensitivity to oxytocin, and a 10- to 20-fold increase in prolactin levels [4]. Experimental models exist, and specific electrophysiologic effects of various hormones have been at least experimentally identified. It is known that progesterone enhances slowly activating delayed rectifier potassium channels (IKs) activity, but that estradiol reduces rapidly activating delayed rectifier potassium channels (IKr) activity [5]. However, multiple effects in any given woman make specific hormonal attribution to arrhythmias complex.

During normal pregnancy, hemodynamic changes are seen including an increase in blood volume, decrease in blood pressure, decrease in peripheral resistance, and an increase in arterial compliance. The mechanisms for these physiologic effects are complex, but the effects on vasodilatation appear at least to be in part mediated by nitric oxide (NO). Additionally, hormonal changes in pregnancy regulate the production of NO. Both relaxin, which is produced by the corpus luteum, and estrogen stimulate production of NO [6,7]. While these hormonal and resultant hemodynamic and physiologic changes are well tolerated in the normal heart, in women with congenital or acquired heart disease, pregnancy is associated with high risk of maternal complications. Predictors of poor outcomes include prior history of cardiac arrhythmias, New York Heart Association Class 3−4 heart failure, cyanosis, left ventricular ejection fraction <40%, left ventricular outflow gradient (aortic valve area $<1.5\ cm^2$ or peak gradient > 30 mmHg), or mitral stenosis (mitral valve area $<2\ cm^2$) [8]. Hormonal changes such as increased circulating prostaglandins, atrial naturetic peptides, and endothelial NO have been associated with the decrease in diastolic blood pressure during pregnancy [9].

The large volume expansion of pregnancy and consequent atrial stretch can result in an increase in atrial arrhythmias in vulnerable patients. As the size of the atria

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increases with volume expansion, the atria's geometry may become better suited to sustain a reentrant arrhythmia. Ozmen et al. compared P-wave and QT dispersion during pregnancy in 162 healthy pregnant women, which was compared to 150 healthy nonpregnant women. In addition to performing an electrocardiogram and echocardiogram, they measured estradiol levels in both groups. In addition to the expected hemodynamic changes (increased heart rate, increased left ventricular diastolic diameter, increased left atrial diameter), P-wave dispersion and serum estradiol levels were significantly higher in the pregnant women. The P-wave duration was significantly shorter in the nonpregnant control group. They found no significant differences in the maximum P wavelength and the corrected QT dispersion between the groups. Shortening of the minimum P-wave duration during pregnancy leads to the noted increased P-wave dispersion. In this healthy group of women, no atrial fibrillation was observed. Given the elevated estradiol levels, the authors speculate a causal effect with the shortening of the P-wave and increased P-wave dispersion. They also speculate that in this healthy population, the shortening of the P wave may help maintain the homogeneity of atrial conduction during pregnancy [10] Lechmanova et al. described a different finding with regards the QTc during pregnancy. They noted a prolongation of QTc in pregnant women as compared to healthy controls and concluded a relation between the hormonal changes of pregnancy and QTc prolongation [11].

Autonomic changes in pregnancy and their relationship to arrhythmia

The communication between the autonomic nervous system and the heart is complex. The sympathetic fibers innervating the heart arise from the sympathetic trunk that is composed of the superior cervical, stellate, and thoracic ganglia from the cervical and thoracic spinal cord. Axons arising from the sympathetic trunk become the superior, middle, and inferior cardiac nerves and terminate on the surface of the heart in a heterogenous pattern with more connections formed at the base of the heart relative to the apex. Vagal input to the heart originates in the nucleus ambiguous of the medulla. The preganglionic fibers exit the skull at the jugular foramina and course alongside the carotid arteries and ultimately insert into fat pads on the posterior aspect of the heart, which make up the cardiac plexuses. The postganglionic branches then extend from these plexuses to primarily innervate the sinoatrial node, AV node, and the cardiac conduction system [12]. Through norepinephrine stimulation of beta-1 adrenergic receptors, the sympathetic nervous system activates "funny" pacemaker currents and IKs. The net result of the activation is an increase in conduction velocity, shortened refractory periods, and enhanced pacemaker cell automaticity [13]. Conversely, through the release of acetylcholine, the parasympathetic nervous system stimulates muscarinic receptor M2 that results in a reduced conduction velocity, increased refractory periods, and reduced automaticity [14]. Figs. 59.1 and 59.2 show the changes in pacemaker and myocyte action potential with the addition of sympathetic or parasympathetic stimuli. Under typical physiologic conditions, the complex network of autonomic inputs works in concert to maintain appropriate cardiac and electrophysiologic function. With extremes or distortions of autonomic input, the electrophysiologic properties of myocytes may become arrhythmogenic [15]. In the case of pregnancy, where alterations in autonomic tone take place, this imbalance can predispose women to arrhythmias (Fig. 59.3).

During pregnancy, the balance between parasympathetic and sympathetic tone changes. Through the use of spectral heart rate variability analysis, Speranza et al. found that the low/high-frequency peaks were significantly different in pregnant women compared to nonpregnant controls [16]. The predominant underlying autonomic tone appears to be dynamic and evolves throughout pregnancy. Kuo et al. compared heart rate variability in different trimesters to nonpregnant controls. They found that heart rate variability was increased during the first trimester and

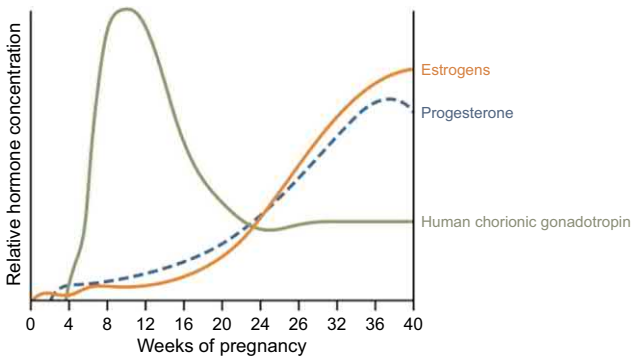

FIGURE 59.1 Estrogen, progesterone, and HCG levels throughout pregnancy [34].

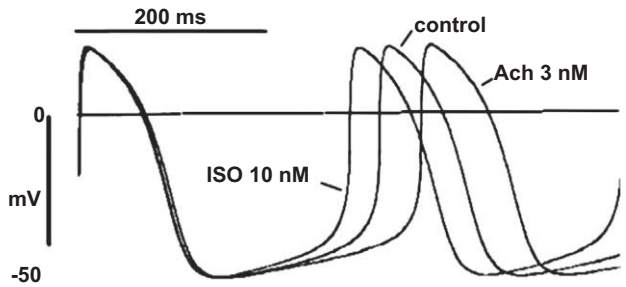

FIGURE 59.2 Comparison of action potentials of cardiac pacemaker cells at baseline, with infusion of isoproterenol to stimulate beta-1 adrenergic receptors and with infusion of acetylcholine to stimulate muscarinic acetylcholine receptor M2 [35].

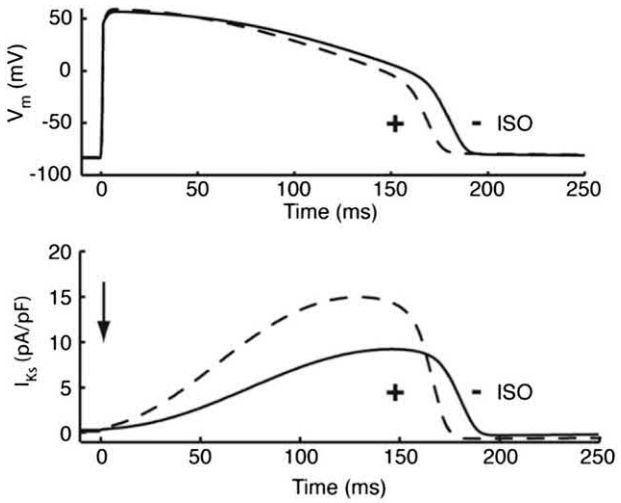

FIGURE 59.3 Changes in the ventricular myocyte action potential and activity of IKs with and without the addition of beta-1 adrenergic receptor stimulation using isoproterenol [36].

became progressively decreased in the second and third trimesters. From this, the authors concluded that autonomic tone is primarily vagal in the earliest stages of pregnancy but by the second trimester has become predominantly sympathetic and becomes increasingly so by the time of delivery. The investigators were also able to demonstrate that the changes appear to be positional dependent. Pregnant women in a right lateral decubitus position had less heart rate variability. The finding is likely explained by the aortocaval compression that can take place at later stages of pregnancy [17]. These autonomic changes appear to be more pronounced during periods of increased physiologic stress beyond that typically experienced in pregnancy. In patients with severe preeclampsia or hypertension, sinoatrial baroreceptor reflex dysfunction has been described [18,19].

As a result of the increasing sympathetic stimulation through the course of a pregnancy, the resting sinus rate will increase. The increase in resting heart rate can be appreciated during the first few weeks of a pregnancy and typically peaks around the 32nd week of pregnancy. Women carrying twins have been noted to have an earlier increase in their resting heart rate [20]. An increase from baseline of approximately 20% has been considered normal [21,22]. The increase in resting heart rate is likely well tolerated in a woman with a normal heart, but in woman with a preexisting heart condition, the relative tachycardia could increase their risk of developing an arrhythmia.

In addition to the changes seen in baseline sympathovagal tone in pregnancy, the body's orthostatic reflex responses to stimuli appear to be blunted. Barron et al. found that woman who are pregnant have smaller increases in their circulating levels of norepinephrine when standing than nonpregnant controls [23]. Baroreceptor reflex dysfunction has been described before likely contributes to the high incidence of orthostatic lightheadedness reported by pregnant women [24,25]. This phenomenon is of particular clinical importance during periods of massive volume loss. When peripartum hemorrhage occurs, the blunted reflex response may lead to inadequate arterial blood pressure and as a result may increase maternal mortality.

Specific arrhythmias in pregnancy

Sinus bradycardia occurs commonly in young women but is relatively uncommon in pregnancy. It can be seen during sleep or in athletes due to a higher vagal tone seen early in pregnancy. In the absence of the disease process, there may be transient bradycardia after delivery and in the postpartum period, which normally improves without any intervention in the absence of prolonged pauses or conduction system disorders. Therapy for sinus bradycardia depends on symptoms and is usually focused on reversing any causes of bradycardia. Medications such as atropine or isoproterenol can be used acutely to improve symptomatic bradycardia acutely. Rarely, a pacemaker becomes during term pregnancy and should be performed with minimal use of fluoroscopy with necessary precautions to decrease radiation [1].

As a result of increased vagal tone early in pregnancy, AV block has been infrequently observed [1]. Transient first-degree AV block can occur during sleep in healthy, young women, and this can increase in pregnancy. Unless there are other conduction system disorders or severe bradycardia accompanying first-degree AV block, there is usually no need for therapy. In patients who have advanced AV block, evaluation for structural heart disease should be performed. The need for pacing is determined by underlying cardiac disease and stability of escape rhythm. If the escape rhythm is unstable, or there is hemodynamic instability with no reversible etiology, pacemaker implantation may be needed with precautions used regarding radiation [26].

A population at particular risk for malignant arrhythmias in the peripartum period is women with long-QT syndrome. The increased risk seems almost exclusive to women with long QT2, and this risk is present for 6 to 9 months postpartum as compared to risk during the pregnancy itself or during the 40 weeks prior to conception [27]. This finding is likely related to both adrenergic and hormonal changes that occur in pregnancy. Patients with long QT2 have a mutation in the KCNH2 gene that encodes the Kv11.1 potassium channel which contributes to the IKr largely responsible for rapid myocyte repolarization. In patients with long QT1 and long QT2, the QTc typically prolongs with increasing sympathetic tone [28]. In studies examining the triggers associated with sudden cardiac death in long QT2, sleep, auditory, and emotional triggers have been identified [29]. The postpartum period is often

associated with altered sleep-wake cycles when caring for a newborn that could increase sympathetic tone and increase the likelihood of sudden death in these patients. Animal models have demonstrated that estrogen reduces the expression of beta-1 adrenergic receptors. Estrogen and progesterone levels are high during pregnancy but decrease below normal levels postpartum during breast feeding. The abrupt change in estrogen levels following delivery could result in a more robust response to sympathetic tone, increasing the likelihood of arrhythmia in long-QT patients [30].

Catecholaminergic polymorphic VT is typically triggered by exertion or emotional distress. Despite the theoretical risk of increasing arrhythmia risks due to the adrenergic disturbances associated with pregnancy, Cheung, et al. demonstrated that in a retrospective study looking at 96 patients with catecholaminergic polymorphic VT that the rate of sudden cardiac death was no higher in pregnancy or in the postpartum period compared to nonpregnant rate [31].

Makhija et al. reported on an interesting case of hormone-sensitive VT during pregnancy. Idiopathic left ventricular VT that was verapamil sensitive occurred during pregnancy in a primigravida woman. She was treated with verapamil and underwent EP testing postpartum. At baseline, she was not inducible, but administration of progesterone facilitated induction and ablation of the arrhythmia. While this is an unusual circumstance, the relation to hormonal effects of pregnancy is likely [32].

Another potential link noted between sex hormones and sudden cardiac arrest was noted in the Oregon Sudden Unexpected Death Study. The authors found significantly lower SCA risk in patients with higher testosterone levels. But higher estradiol levels were associated with a higher SCA risk in both men and women [33].

Conclusion

The mechanism by which the changes in circulating sex hormone levels and autonomic nervous system lead to a slightly increased risk of arrhythmia is poorly understood. This is largely due to the lack of available data due to difficulty performing electrophysiology studies in pregnant women. Limited instances of electrophysiologic testing performed with infusion of sex hormones provide insight into their effects on the electrophysiologic properties of cardiac cells. The effect the autonomic changes which occur in pregnancy have on the cardiac action potential is less clear. Inferences can be made about why these changes lead to arrhythmia by considering the effects changes in sympathetic or vagal tone have on nonpregnant individuals. However, these inferences are of limited value as the autonomic changes that take place during pregnancy are more complicated and the effects of the hormonal milieu alter the response myocytes may have when subjected to varying degrees of autonomic tone.

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Chapter 60

Supraventricular tachycardia in pregnancy

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Introduction

Supraventricular tachycardias comprise a heterogenous group of cardiac tachyarrhythmias arising above the level of His–Purkinje system with atrial or ventricular rates exceeding 100 beats per minute [1]. SVT can occur in pregnant patients with or without preexisting structural heart disease and can present for the first time in pregnancy or as a recurrence in patients with a previous history of SVT. While generally considered benign, recent data suggest SVT in pregnancy can be associated with adverse maternal and fetal outcome, especially in women with preexisting structural heart disease [2–6]. The management of SVT in pregnancy can be challenging due to the risks of medical and nonmedical therapies to the expectant mother and fetus, and the paucity of randomized controlled trials to guide management of these patients. In this chapter, we review the clinical impact and epidemiology of SVT in pregnancy, followed by the clinical manifestations and investigations, and finally discuss the management centered on the best available evidence (Fig. 60.1).

As detailed in previous chapters, SVT is a term comprising several heterogenous disorders. These include rhythms that involve a part or the entirety of the AV node in a circuit—such as atrioventricular nodal reentrant tachycardia (AVNRT), orthodromic or antidromic reciprocating tachycardia through an accessory pathway (atrioventricular reentrant tachycardia/AVRT), junctional tachycardia (JT), or rhythms not dependent on the AV node such as atrial tachycardia (AT) and intraatrial reentrant tachycardia (IART). While atrial fibrillation (AF) and atrial flutter are technically supraventricular tachycardias, the workup and management of these rhythms is distinct from SVTs, and these rhythms are discussed separately in the next chapter. Preexcited AF is a chaotic rhythm characterized by rapid anterograde conduction of AF down a manifest accessory pathway and can also occur in pregnancy.

Physiological changes in pregnancy and electrophysiology of SVT

Multiple physiological changes in intravascular volume, sex hormones, autonomic tone, and electrophysiology can increase the susceptibility of pregnant women to arrhythmias and impact the clinical management of SVT in pregnancy [7,8]. These changes are reviewed in detail in Chapter 57. These changes can have complex effects on the electrophysiological mechanisms of various cardiac arrhythmias.

The total plasma volume increased by 150%, and total body water by 5–8 L increasing the cardiac end diastolic volume, stroke volume, and cardiac wall stress. Increase in circulating plasma volume is reflected in the increased jugular venous pressure present on physical examination. Stretch-related ionic channels can activate resulting in atrial and ventricular premature complexes, which can initiate or constitute cardiac arrhythmias. Along with plasma volume, the maternal heart rate also increases contributing to elevated cardiac output in pregnancy. Obstructive lesions such as mitral stenosis, which depend on a longer diastolic filling period to maintain hemodynamic stability, may not be tolerated in due to these physiologic changes resulting in heart failure and SVT. Furthermore, automatic SVTs such as certain ATs may be suppressed by the increased sinus rate during pregnancy. Pregnancy is a state of heightened sympathetic activity, and triggered arrhythmias that depend on increased sympathetic activity and elevated heart rates

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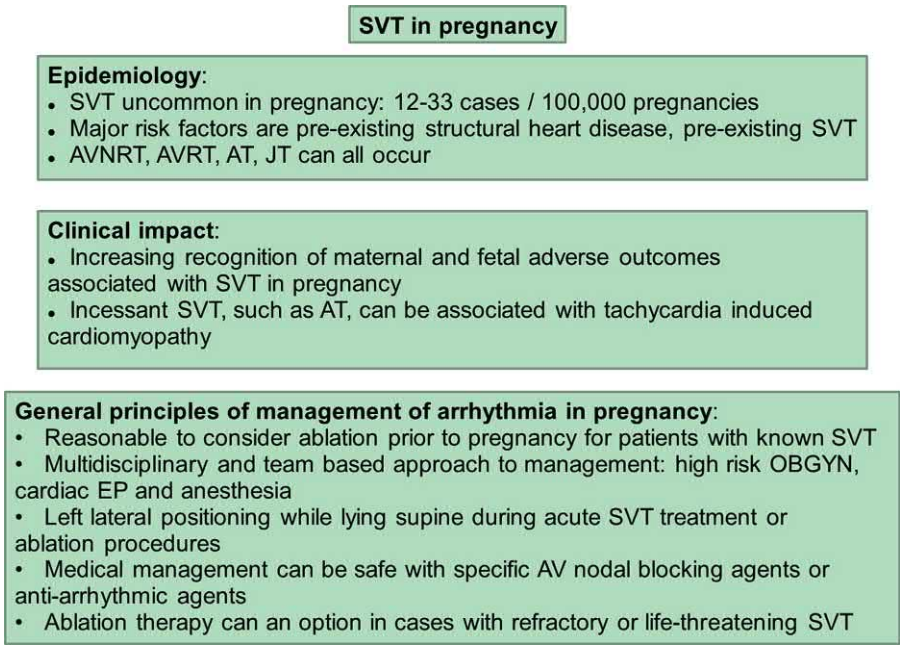

FIGURE 60.1 Overview of SVT in pregnancy.

may become more common [9,10]. During labor and delivery, the converse could be present, due to vagally mediated reductions in heart rate.

The pharmacokinetics of antiarrhythmic medications are altered by the changes in total body distribution, plasma protein concentration, gastric motility, and pH and renal blood flow [11]. Antiarrhythmic pharmacotherapy in pregnancy is reviewed in depth in Chapter 72.

Clinical impact and maternal and fetal prognosis of SVT in pregnancy

Maternal mortality and cardiovascular disease

Maternal mortality has been steadily increasing in the United States. Over the course of 22 years (from 1987 to 2009), for every 100,000 pregnancies, the maternal mortality increased from 7.2 to 17.8 [12]. Creanga et al. found that although traditional causes of pregnancy-related mortality continued to decline from 2006 to 2010, cardiovascular causes increased by 26.4%. Cardiac arrhythmias, including SVT, AF, and ventricular tachycardia are all important contributors to maternal cardiovascular morbidity and mortality. In a large administrative dataset, hospitalization for arrhythmia in pregnant women led not only to a higher rate of in-hospital death, 5.9% (compared with 0% in all women), but also led to a higher rate of maternal or fetal complications, 36.5% (compared to 21.8% in all women) [5].

Maternal and fetal outcomes in SVT

In a nonpregnant patient, SVT is reported to have a relatively benign course and SVT in pregnancy is conventionally believed to have a benign outcome. However, in pregnant women, there is growing data implicating the association of SVT with poor maternal and neonatal outcomes. Siu et al. retrospectively reviewed 252 pregnancies from 205 women who had congenital 137 (55%), acquired 87 (34%), or arrhythmic (11%) cardiac disease and noted that a maternal cardiac event, neonatal event, or both occurred in 71 pregnancies (28%) [4]. Most cardiac events (89%) occurred in the antepartum period and were either heart failure or cardiac arrhythmia (largely SVT). Silversides et al. also examined arrhythmias and their impact on maternal and fetal outcomes. In their analysis of 73 women, a background of SVT was present in 36 pregnancies. Adverse fetal events developed more commonly in women who had antepartum arrhythmias (relative risk 3.4, 95% confidence interval 1.0−11.0, $P = .045$) [3]. Although this analysis did group all SVT/VT/AF/AFL together, fetal adverse events were present in three (8%) of those with SVT.

Recent registry data from Taiwan showed that in a total cohort of 2,350,328 women with structural heart disease, 769 women experienced SVT during pregnancy. In comparison with a reference group, SVT in pregnancy was associated with greater odds of severe maternal morbidity,

cesarean delivery, low birth weight, preterm labor, fetal stress, and fetal abnormalities [6]. More recently, the CARPREG II Study was published on 1938 pregnancies (which contained a heterogeneous population of mothers with structural and nonstructural cardiac disease), cardiac arrhythmias were common (9.25%), with two deaths related to SVT in patients with preexisting structural heart disease [2].

Fetal prognosis in maternal SVT

In reviewing these data and applying it to patients, it is imperative to note that patients with preexisting structural cardiac disease (such as congenital heart disease) are often grouped with patients with structural normally hearts for the analysis. This must be taken into consideration when discussing with pregnant mothers and their families. Adequate uteroplacental blood flow is a vital requirement for nutrient and oxygen supply to the developing fetus, and alterations in uteroplacental blood flow are associated with the birth of small-for-gestation fetuses [13]. Although pregnant patients with structurally normal hearts may be able to sustain an adequate cardiac output for placental perfusion during SVT, those with preexisting structural abnormalities, or incessant tachycardia even with a structurally normal heart, may be at risk of reduced uteroplacental flow and the attendant risk of intrauterine growth restriction. Indeed, among pregnant women with preexisting heart disease, reduced maternal cardiac output and abnormalities in fetal umbilical artery flow detected by Doppler ultrasonography were independent predictors of adverse neonatal outcomes. Thus, the likelihood of reduction in placental perfusion due to SVT, due to factors such as maternal structural heart disease or incessant tachycardia, must be considered while counseling pregnant women regarding the risk to the fetus from the SVT. The mechanism of tachycardia may indicate the presence of underlying structural heart disease and could guide an estimation of prognosis. For example, dual atrioventricular nodal physiology and AVNRT are commonly seen in structurally normal hearts. However, AF and IART are extremely uncommon in the absence of structural heart disease. Presence of these rhythms may indicate a worse fetal prognosis ascribable to maternal structural heart disease.

Epidemiology of SVT in pregnancy

SVT is overall uncommon in pregnancy, but it is important for treating physicians to be aware of the epidemiology and risk factors for SVT in view of the potential adverse effects on the mother and fetus. Studies report that the overall frequency of SVT in pregnancy is 12–33 out of 100,000 pregnancies, and that the frequency of SVT in pregnancy is table over time [5,14]. Although tachyarrhythmias are one of the more common cardiac complications of pregnancy, certain risk factors can increase the risk of developing SVT [5,14]. In a large administrative dataset, women with increasing ages from 41 to 50 had greater prevalence of arrhythmias [5]. Increasing pregnancy rates among older women could be contributing to the rising arrhythmia burden in pregnancy [15]. Arrhythmias were also found to be more frequent in African-American women compared to Caucasian women. Another risk factor for arrhythmia in pregnancy is preexisting structural or congenital heart disease. As treatments for congenital heart disease improve, more women with repaired congenital heart disease are becoming pregnant, thus leading to an increased rate of tachyarrhythmias including SVT [16–18]. Patients with a known substrate for arrhythmias and congenital arrhythmogenic syndromes, such long QT syndrome, are also at higher risk for tachyarrhythmias during pregnancy [17].

There have been many studies examining whether the risk of first onset of arrhythmia is increased in pregnancy; however, results have been inconclusive. For example, although Lee et al. found no significant increase in the first onset of SVT during pregnancy upon analyzing 207 women, over a 2-year analysis Tawam et al. found an increased risk of the first presentation of SVT during pregnancy [19,20]. However, data are more supportive of increased recurrences of SVT during pregnancy among those with a preexisting diagnosis of SVT [19,21].

Many different types of supraventricular arrhythmias can occur during pregnancy. Atrial premature beats during pregnancy are extremely common, with one study showing a prevalence of 57% [22]. AVNRT is considered the most common, but AVRT, JT, and AT can all occur. Focal AT in pregnancy can be incessant and cause tachycardia-mediated cardiomyopathy [8]. Common sites for AT in pregnancy include the crista terminalis and the atrial appendages [23–26]. Appendage-related AT can result in incessant AT and heart failure and can be associated with anatomical abnormalities such as appendage diverticula that increase the complexity of catheter ablation, necessitating even surgical intervention at times [27].

Clinical evaluation

History

Women with or without a past medical history of SVT can present with arrhythmia in pregnancy. Pregnant women present with similar complaints to nonpregnant patients with SVT. However, the intensity of symptoms may be different in pregnancy, such that previously well-tolerated or minimally symptomatic arrhythmias now cause unbearable symptoms or hemodynamic instability. This may relate to changes in maternal hemodynamics including an

increase in cardiac output and plasma volume. For example, in patients with AVNRT, presence of cannon A waves may be particularly uncomfortable in the later trimesters of pregnancy when the jugular venous pressure is elevated. Particular complaints can include palpitations, presyncope, syncope, dyspnea, and/or chest pain. Although syncope is possible, it is an uncommon presentation for SVT and should raise concern for underlying structural heart disease or ventricular tachycardia. One caveat to note is the palpitations are a common complaint among pregnant women and its correlation with arrhythmias is weak [22].

The onset and offset of palpitations can be an important means to distinguish between types of SVT. A sudden, abrupt, onset is suggestive of a paroxysmal tachycardia such as AVNRT, whereas descriptions of the tachycardia gradual warming up and slowing may be more consistent with an atrial or sinus tachycardia. If the tachycardia terminates with Valsalva maneuver or carotid sinus massage, this could suggest AVRT or AVNRT.

When also taking a history it is important to note any congenital or structural heart disease history and any surgical corrections, as we have discussed these patients tend to have suboptimal outcomes.

Physical examination

A complete physical examination is essential and may alert the clinician to underlying structural heart disease and heart failure. The physical examination in a patient in SVT may reveal a rapid pulse which may be regular or irregular depending on the underlying cardiac rhythm. Cannon A waves may be present in those with AVNRT. Findings suggestive of underlying structural heart disease include elevated jugular venous pressure, harsh systolic murmurs, or diastolic murmurs.

Role of ECG

ECG changes occurring during pregnancy are important to understand. Different changes have been reported across different trimesters, and although published studies have not been consistent, the key take away point for a physician interpreting an ECG in a pregnant lady is that there is a wide variation in normal. These alterations are extensively discussed in Chapter 57 of this text.

12-lead ECG during SVT, or telemetry, can aid in the diagnosis of the mechanism of SVT. Although exceptions exist, SVTs with a regular ventricular response can be AVNRT, AVRT, or AT and SVTs with irregular ventricular response are usually AT or atrial flutter with variable AV block or AF. For SVTs with regular ventricular response, P waves can be discernible with close attention to the ECG. In general, long R-P tachycardia are due to AT, while short R-P tachycardia are AVNRT or AVRT. Preexcited AF presents as an irregular wide complex and chaotic appearing rhythm. Adenosine administration can assist in the diagnosis of SVT mechanism by either slowing the ventricular rate or terminating the arrhythmia, suggesting an AV node–dependent mechanism.

Among patients with complaints of palpitations, but no documentation of SVT on telemetry or 12-lead ECG, ambulatory ECG monitoring should be considered. This may include noninvasive options such as 24 or 48 h Holter monitors or event monitors. For those with infrequent but bothersome symptoms, implantable loop recorders may be considered.

Echocardiography

Echocardiography is an essential element to the evaluation of a pregnant patient with SVT. It is safe in pregnancy and can be invaluable in characterizing underlying structural heart disease.

Management of SVT in pregnancy

General principles

While treatment of SVT in nonpregnant adults is guided by multiple studies and extensive clinical experience, there is a paucity of data pertaining to nonmedical and medical therapy guiding management of SVT in pregnancy. Certain general principles of nonmedical and medical arrhythmia management in pregnancy can guide therapy. First, for women with known SVT who are planning a pregnancy, it is reasonable to perform an ablation procedure for definitive management of the SVT prior to pregnancy [8]. Second, a multidisciplinary and team-based approach, involving high-risk obstetrics, cardiac electrophysiologists, anesthesiologist ,and the most important team member, the patient, is crucial in successfully managing SVT in pregnancy. Third, when lying supine, the gravid uterus can cause aortocaval compression resulting in reduction of preload and increase in afterload. A left lateral position or leftward tilt by 30 degrees can aid hemodynamics when managing a patient with acute SVT or during ablation. Fourth, although there is a paucity of well-controlled randomized trials demonstrating the safety of AV nodal blocking and antiarrhythmic medications in pregnancy, it is important to be aware of the available data regarding the safety of these drugs and the general principles of pharmacotherapy in pregnancy (discussed in Chapter 72). Most commonly used AV nodal blocking and antiarrhythmic medications are either FDA class C or D, and the lowest effective dose should be used (Table 60.1). Medical management of SVT in pregnancy can be safe and efficacious while bearing these principles and data in mind. Finally, while ablation therapy is safe and efficacious in treatment of nonpregnant patients with SVT,

TABLE 60.1 Pharmacotherapy of SVT in pregnancy [11,41].

Drug	Antiarrhythmic class	US FDA pregnancy category[a]	Maternal adverse effects	Fetal adverse effects
Procainamide	IA	C	Lupus like syndrome with long-term administration	As a weak base, can be trapped in fetal blood which has slightly acidic pH
Flecainide	IC	C	Visual disturbances, acute interstitial nephritis, VT in structural heart disease	Not reported, used for fetal SVT
Propafenone	IC	C	VT in structural heart disease	Rare, data limited to few reports. No teratogenicity in animal studies
Metoprolol	II	C	Bradycardia	Fetal bradycardia, IUGR
Propranolol	II	C	Bradycardia, tocolytic	Fetal bradycardia, IUGR, intravenous administration during labor can cause fetal respiratory distress after birth
Sotalol	III	B	Bradycardia, prolonged QTc	Used for fetal SVT
Dofetilide	III	C	Prolonged QTc	In animal studies, fetal developmental abnormalities noted
Amiodarone	III	D	Hypo- or hyperthyroidism, toxicity less likely due to short duration courses	Congenital goiter, hypothyroidism, neurodevelopmental abnormalities
Verapamil	IV	C	Bradycardia	Fetal bradycardia, no evidence of teratogenicity
Diltiazem	III	C	Bradycardia	In animal studies, high doses resulted in embryotoxicity
Digoxin	NA	C	Nausea, visual disturbances	No teratogenicity
Adenosine	NA	C	Dyspnea, bronchospasm	Unlikely due to short half-life

A, well-controlled studies demonstrating no risk to fetus; *B*, animal studies demonstrating no risk to fetus with no controlled studies in humans; *C*, either animal studies demonstrating adverse effects to fetus with no controlled studies in humans or no studies available in animals or humans; *D*, evidence of human fetal risk based on studies, but with potential benefits that may warrant use of the drug in pregnancy despite the risks; *VT*, Ventricular tachycardia; *IUGR*, intrauterine growth restriction; *X*, risks in pregnancy outweigh the benefits.
[a]*US FDA (United States Food and Drug Administration) Pregnancy Risk Categories.*

there are concerns over ablation during pregnancy due to fetal risk from radiation and fetal compromise as a result of the ablation procedure itself. However, ablation employing nonfluoroscopic techniques can be performed at tertiary care centers in those with repeated episodes of SVT uncontrolled by medical therapy [24,28].

Acute management of SVT (Fig. 60.2)

Pregnant patients with acute onset of SVT can present during any trimester in pregnancy or during labor. Since the rapid ventricular rates in SVT can impair placental perfusion and could threaten the fetus, termination of the SVT is critical. The first steps are similar to management of most medical emergencies, with an assessment of the patient's airway, breathing, and circulation [29]. Telemetry and 12-lead ECG will aid diagnosis of the rhythm and monitoring response to therapy. Fetal monitoring should be employed when possible to assess the impact of the SVT and the acute therapies on the fetus.

The first-line management of SVT includes vagal maneuvers, such as forced expiration against a closed glottis, carotid massage after the exclusion of ipsilateral bruit, or application of a cold towel to the face [1,8]. The second-line management involves the use of AV nodal blocking agents which can terminate AV nodal dependent SVTs and aid the diagnosis of AT or flutter [30]. Adenosine is the first choice drug, is unlikely to affect the fetus due to its extremely short half-life, and there are a number of observational reports supporting its efficacy and safety [31]. Adenosine is administered as a rapid IV bolus of 6 mg, with up to two additional doses of 12 mg. In cases with adenosine failure, IV beta-blockers such as metoprolol or propranolol, or IV calcium channel blockers such as verapamil or diltiazem, can be attempted. IV procainamide can be used as a third-line agent in those with refractory SVT.

In patients with hemodynamic compromise at presentation, or for those with SVT refractory to AV nodal blocking agents, synchronized DC cardioversion is recommended, and considered safe. Uterine contractions can be triggered by cardioversion, and pads must be applied including the maternal heart in the cardioversion vector while avoiding the uterus. The ACC/AHA guidelines recommend energy dosing similar to nonpregnant patients [1].

Chronic management of SVT (Fig. 60.3)

After SVT is terminated, a complete history, physical examination, and investigations as outlined previously are essential and can guide further management. The objective is to prevent future episodes of SVT, in general utilizing pharmacotherapy as first line and catheter ablation as second line, while avoiding maternal and fetal adverse effects.

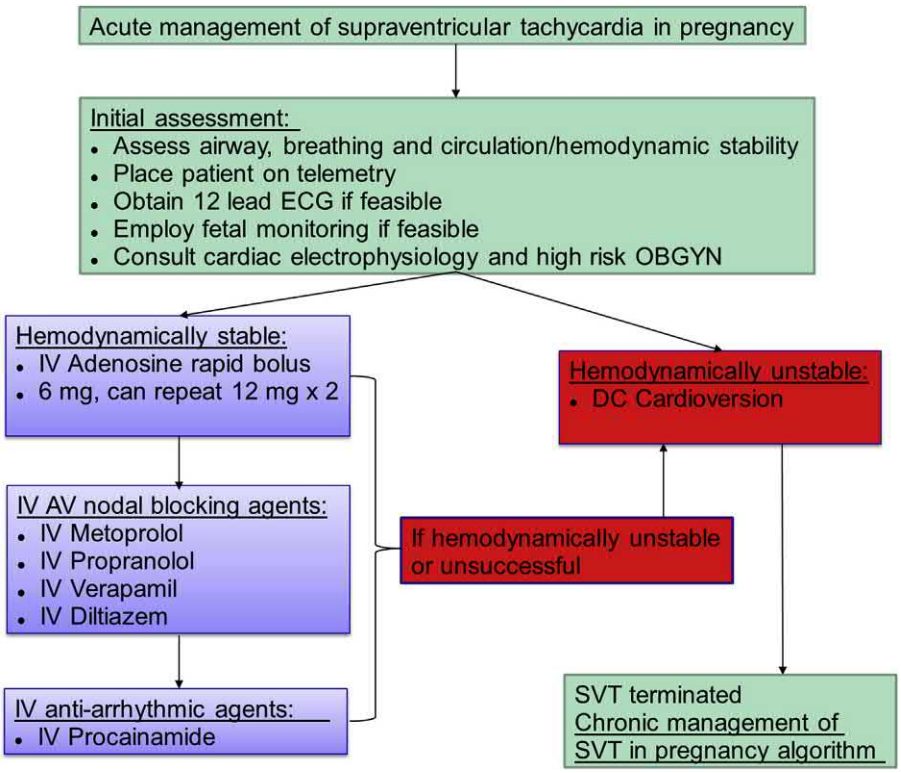

FIGURE 60.2 Flowchart of acute management of SVT in pregnancy.

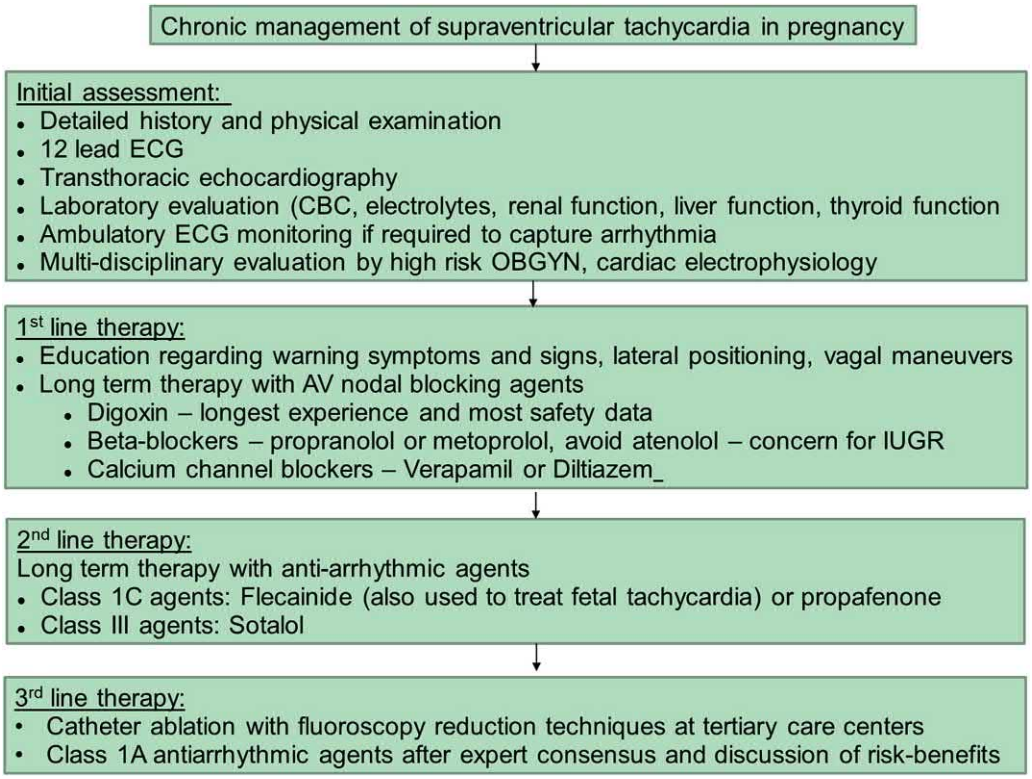

FIGURE 60.3 Flowchart of chronic management of SVT in pregnancy.

In the first trimester, the fetal teratogenic and overall risk is maximum, and there are scant data regarding the safety of pharmacotherapeutic agents, necessitating management on a case-by-case basis. Among the AV nodal blocking agents, digoxin has been utilized for decades and is efficacious as a first-line agent for prevention of SVT and also used for fetal tachycardia [11,32]. While oral beta-blockers such as propranolol and metoprolol are considered safe for the mother, there are concerns over intrauterine growth restriction, mainly with long-term use and courses starting earlier in gestation [33,34]. Among antiarrhythmic agents, flecainide is considered safe and efficacious and is also used to control fetal tachycardia. Propafenone and sotalol are also considered safe, while there is minimal data on newer antiarrhythmic agents such as dofetilide. Oral amiodarone can result in fetal hypothyroidism and is generally not recommended unless other medical and nonmedical options are exhausted.

In nonpregnant patients, catheter ablation is safe, efficacious, and considered the first-line therapy for most SVTs. Concerns over maternal and fetal adverse effects due to radiation, and procedural considerations, limit the use of catheter ablation to pregnant patients with recurrent SVT despite medical therapy, and life-threatening SVT. Similar to radiation damage in adults, harm to the fetus can be dose dependent (low risk $\leq$50 mGy) or stochastic. Studies estimate the radiation dose to the conceptus with a typical catheter ablation procedure as $<$1 mGy in all trimesters of pregnancy, and ranging between 0.0023 and 0.012 mGy/min [35–37]. The stochastic effect of an increase in childhood cancers was estimated as very small. Although the practice of draping the mother's abdominopelvic region with a lead apron is common, these studies do not demonstrate a decreased radiation dose to the fetus. This is likely because most of the radiation to the fetus is secondary to scatter from the maternal thorax. However, it is difficult to rule out minor biological benefits and a potential psychological benefit to the mother.

With the advent of electroanatomic mapping, increasing trends and clinical experience with nonfluoroscopic ablation, there are several case reports and retrospective series detailing successful and safe ablation of SVT during pregnancy [24,28,38,39]. While fluoroscopy use was common in earlier studies, newer studies are reporting increasing use of electroanatomic mapping to eliminate or greatly reduce fluoroscopy time. Intracardiac echocardiography can be extremely helpful with catheter visualization, and transseptal access under intracardiac echocardiography guidance has been successfully performed without fluoroscopy in pregnant patients [40]. While most cases report use of radiofrequency energy, successful cryoablation has also been reported [39].

Multidisciplinary evaluation of the pregnant patient with SVT, involving high risk OBYGN, cardiac electrophysiology, and anesthesia should occur prior to proceeding with catheter ablation for SVT. There should be a detailed discussion with all team members including the anesthesia staff regarding conscious sedation versus general anesthesia and patient positioning prior to starting the procedure. Fetal monitoring should be employed to detect fetal distress early. There must be facilities and mechanisms available for emergency caesarean section, should the need arise, at gestational ages where the fetus is deemed viable.

Conclusions

Maternal morbidity and mortality is on the rise and cardiac conditions, including arrhythmias, are increasing contributors to this trend. SVT is considered benign but there are increasing data suggesting adverse maternal and fetal outcomes in pregnant women with SVT. Detailed history, physical examination, and investigations such as ECG and echocardiography are critical in the management of these patients. Medical and nonmedical management of SVT in pregnancy can be safe and effective, with attention to general principles of arrhythmia management in pregnancy, and knowledge of the available data on antiarrhythmic safety and efficacy. For patients with recurrent SVT despite medical therapy or life-threatening SVT, catheter ablation using nonfluoroscopic techniques is increasingly reported and can be safely utilized by multidisciplinary teams in tertiary care centers.

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Chapter 61

Atrial fibrillation in pregnancy

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Introduction

Atrial fibrillation (AF) is the commonest supraventricular arrhythmia, and its prevalence is associated with advanced age and the presence of structural heart disease or hypertension [1]. On the other hand, incidence of self-reported palpitations during pregnancy can be as high as 12% [2], whereas presence of ectopic systoles in Holter monitoring is not rare [3]. In this context, AF may manifest for the first time or become more frequent during pregnancy, especially in older pregnant women. Importantly, prevalence of AF in pregnancy is expected to increase due to the increasing mean age of conception and the number of patients with congenital heart disease reaching childbearing age [4].

Epidemiology and impact of atrial fibrillation during pregnancy

To date, few studies have been conducted in pregnant women with AF. It is well known that pregnancy may exacerbate supraventricular tachycardias [5] and that there is a high incidence of ectopic activity in healthy pregnant women who often present symptoms, mostly palpitations. However, these symptoms are usually benign and are not predictive of complex cardiac arrhythmia [3].

In general, AF during pregnancy is an indication of underlying organic heart disease. AF in a structurally normal heart during pregnancy is very rare with a reported prevalence of 0.06%, particularly met at late pregnancy and in older women [6,7]. However, a long-lasting cumulative effect of pregnancy-induced physiological alterations on AF pathogenesis, even in women free of heart disease, cannot be excluded, as a recent publication from the Women's Health Study indicated that risk of AF in women aged $\geq$45 years old was independently associated with increasing number of pregnancies [8].

One of the largest epidemiological studies that examined AF in pregnancy is the report from Lee et al. [6], which included 264,730 pregnancies in the Southern California area. AF was noted in 157 pregnancies, which corresponds to 59.3 cases per 100,000 pregnancies. AF was more frequent in white women and in older maternal age. Moreover, preexisting hypertension, hyperlipidemia, diabetes, and higher preconception body mass index were more frequent among pregnant women with AF compared with women without AF [6]. Odds of AF episodes were higher during the third trimester compared with the first, whereas 12 of the 29 cases observed during the third trimester occurred within 24 h of delivery, probably due to labor-associated hemodynamic changes [6]. Adverse maternal cardiac events were rare in AF pregnant women, since only two patients who developed heart failure were reported. There were no strokes or maternal deaths [6]. Importantly, major fetal complications were similar in women with and without AF and reported as infrequent; also, there was no significant difference in birth weight. In contrast, the rate for neonates admission to the neonatal intensive care unit was higher among AF mothers. However, since the study refers to the general population, and the vast majority were healthy women, the findings cannot be extrapolated in pregnant women with structural heart disease [6].

Another important study is the Registry Of Pregnancy And Cardiac disease (ROPAC), which included 1321 pregnancies in women with heart disease from 28 countries. Of 1321 pregnant women, 7 (1.3%) developed AF or atrial flutter (Afl) during pregnancy, and the majority of AF/Afl episodes occurred during gestational weeks 23–30 [9]. The prevalence of AF/Afl was higher in the ROPAC population, as expected, taking into account the presence of structural heart disease in the enrolled women. As opposed to the study by Lee et al. investigators reported that AF/Afl during

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pregnancy was associated with several unfavorable outcomes, namely, increased maternal mortality, lower adjusted mean birth weight, and higher rates of neonates weighting less than 2500 g [9]. Predictors of AF/Afl onset in the univariate analysis were the history of AF/Afl before pregnancy, mitral valve disease, the presence of left-sided heart lesions, and β-blocker use [9].

Risk factors and concomitant cardiovascular diseases

AF can occur in pregnant women with structurally normal hearts [6]. Nevertheless, it is more common in women with heart disease, such as rheumatic or valvular heart disease, peripartum cardiomyopathy, hypertrophic cardiomyopathy, and congenital heart disease.

Sparse data suggest that the incidence of AF in pregnancy due to rheumatic valvular heart disease has increased in western healthcare systems, probably due to immigrants from countries that still have high rates of rheumatic fever [10]. Moreover, AF may accompany peripartum cardiomyopathy with a prevalence can reach 10% in these patients [11]. Regarding pregnant women with hypertrophic cardiomyopathy, a recent publication from ROPAC study reported that only 1 patient of 60 developed AF during pregnancy [12]. Following repair of congenital heart disease (CHD), it is not uncommon for female patients to reach childbearing age [13], whereas it is of note that AF occurs with increasing prevalence and at a younger age in these patients [14]. Besides the known risk factors for AF, adults with CHD carry the additional factors of the underlying heart defect such as myocardial scarring and fibrosis, patches/scars from heart surgery, and potential chronic oxygen desaturation [14].

There are several concomitant conditions such as hypertension, hyperlipidemia, diabetes, and increased maternal age that have been found to be in higher proportion among pregnant women with AF compared with those without [6]. Pregnancy-related hypertensive disorders could contribute to development of AF through left atrial stretching due to increased hemodynamic load [15,16]. In addition, Scantlebury et al. found that middle-aged women with AF had increased rates of hypertensive disorders during pregnancy compared with controls without AF [17].

Metabolic disturbances such as hyperthyroidism [18], electrolyte imbalances, and alcohol abuse can also contribute to the development of AF during pregnancy [19]. In addition, evidence from case reports indicates that AF in pregnancy may be precipitated by drugs, such as terbutaline and nifedipine administered during tocolysis [20,21].

Pathophysiology of atrial fibrillation during pregnancy

The precise mechanism of increased arrhythmia burden during pregnancy is unclear, but it has been attributed to hemodynamic, hormonal, and autonomic changes related to pregnancy [22].

Physiological adaptation in hemodynamic indices is important to meet the increased metabolic demands of the mother and fetus. Subsequent changes include increased blood volume, cardiac output, and heart rate [23] resulting from the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system [24], both of them being well-known AF promoters [15,16]. Plasma volume and cardiac output (CO) reach a maximum of 40%−50% above baseline at 32 weeks of gestation [4]. The increase in CO is achieved primarily by an increase in stroke volume in early pregnancy and a gradual increase in heart rate in late pregnancy [4]. The increase in plasma volume augments the preload on the ventricles and increases both atrial and ventricular size, contributing to arrhythmogenesis. The electrical consequences of atrial stretch contribute to both the initiation and maintenance of AF. Stretch-activated ion activity is most responsible for early afterdepolarizations, shortened refractoriness, slowed conduction, and spatial dispersion of refractoriness and conduction. Also, the increase in heart rate has been associated with markers of arrhythmogenesis such as late potentials, premature ventricular contractions, and depressed heart rate variability [22,25].

Few studies have been published on the influence of hormonal and autonomic changes on arrhythmogenesis in pregnancy. Pregnancy is characterized by increased levels of estrogen and progesterone, which can also modulate remodeling of the myocardium, particularly cardiac hypertrophy [26,27]. Adrenergic responsiveness seems to be increased in pregnancy, whereas estrogen has been shown to increase the number of myocardial α-adrenergic receptors. This increased adrenergic activity may contribute to enhanced automaticity and triggered activity [22].

Another mechanism that potentially mediates AF pathogenesis in pregnancy is the cardiogastric interaction. An association between gastroesophageal reflux disease (GERD) and AF has been proposed, mainly due to the close vicinity of the esophagus and the left atrium [28]. Elevated progesterone levels may lead to alterations in gastrointestinal motility, and the prevalence of GERD has been reported to be up to 80% in pregnant women, thus suggesting a possible mechanism for AF development [29]. Fig. 61.1 summarizes potential mechanisms that increase AF prevalence during pregnancy.

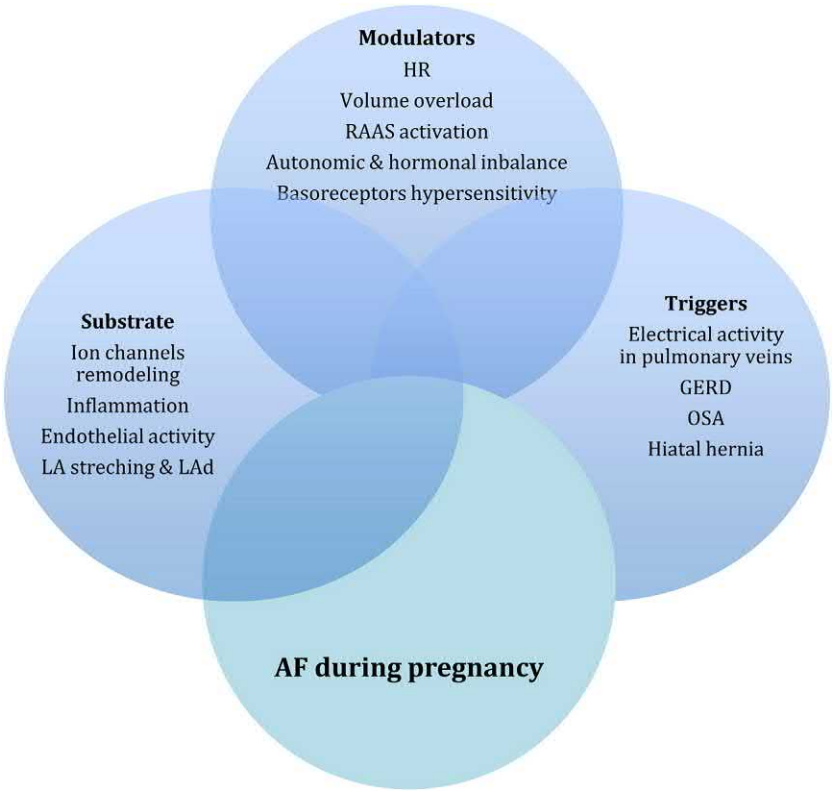

FIGURE 61.1 Mechanisms leading to increased prevalence of atrial fibrillation during pregnancy. *AF*, *atrial fibrillation*; *GERD*: gastroesophageal reflux disease; *HR*: heart rate; *LA*; left atrial; *OSA,* obstructive sleep apnoea.

Pregnancy is also associated with a series of hemostatic changes, with an increase in concentration of coagulation factors, fibrinogen, and platelet adhesiveness, as well as diminished fibrinolysis, which lead to hypercoagulability and, in patients with AF, increase further the risk of thromboembolic complications [4,23].

Classification of atrial fibrillation in pregnancy

AF patterns in a pregnant patient are similar to that in the nonpregnant patient. According to the presentation, duration, and spontaneous termination of AF episodes, five types of AF are traditionally distinguished: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF (Table 61.1) [1].

Clinical presentation

During pregnancy, AF can lead to hemodynamic compromise and result in an increased risk for the mother and fetus. The increased cardiac demand during pregnancy may cause AF to be less well tolerated [6]. Clinical presentation and hemodynamic consequences of AF depend on many

TABLE 61.1 Patterns of Atrial Fibrillation (AF).

AF pattern	Definition
First diagnosed AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia
Paroxysmal AF	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days
Persistent AF	AF that lasts longer than 7 days
Long-standing persistent AF	Continuous AF lasting for ≥1 year when it is decided to adopt a rhythm control strategy
Permanent AF	AF that is accepted by the patient (and physician)

variables including the underlying heart condition and the associated ventricular response rate. In women with heart failure, rheumatic valvular disease, congenital heart disease, or a rapidly conducting antegrade accessory pathway, AF may have serious hemodynamic consequences [9,13,14,18].

Pregnant patients with AF may have a heterogeneous clinical presentation, occurring in the presence or absence of related symptoms. They can experience a variety of symptoms including palpitations, dyspnea, chest tightness, fatigue, and sleeping difficulties. With respect to symptom assessment, the European Heart Rhythm Association (EHRA) suggested the EHRA symptom scale to describe the impact of AF according to symptom severity and daily activity [1]. Less commonly, patients may present with extreme manifestation of hemodynamic compromise, such as chest pain, pulmonary edema, and syncope.

Besides the hemodynamic consequences, pregnant women with AF are at increased risk of systemic embolism, mainly stroke or transient ischemic attract [1,4].

Diagnostic approach to atrial fibrillation in pregnancy

The evaluation of a pregnant women with new-onset AF should focus on the examination of underlying cardiac structural disorders, since these should be present in most cases.

Initial diagnostic workup includes at a minimum a detailed history and meticulous physical examination. In addition, evaluation should involve the following.

A 12-lead electrocardiogram is indispensable to verify the presence of AF and distinguish AF from other atrial arrhythmias. It may also be used to measure and follow PR, QRS, and QT intervals during the treatment with antiarrhythmic agents. Electrocardiogram should be reviewed by an experienced cardiologist or electrophysiologist for preexcitation and Brugada syndrome.

Basic biochemical analyses include electrolytes and evaluation of renal, hepatic, and thyroid function.

Transthoracic echocardiogram is usually performed to identify the presence of valvular or congenital heart disease, to assess atrial and ventricular size and function, and to document coexistent pulmonary hypertension. Importantly, in cases of AF lasting longer than 48 h, transesophageal echocardiography could play a role in the evaluation of atrial thrombus existence to proceed to cardioversion [1,30].

Additional investigation in selected patients may include ambulatory ECG monitoring, stress test, or other ischemia tests depending on symptoms and concomitant heart disease.

Cardiac magnetic resonance imaging (MRI) may have a role in the evaluation of myocardial function and inflammation as well as in congenital heart disease. According to the American College of Obstetricians and Gynecologists, MRI is not associated with risk and is the imaging technique of choice for the pregnant patient, but they should be used prudently and only when the use is expected to answer a relevant clinical question or otherwise provide a medical benefit to the patient. Although, the use of gadolinium contrast with MRI should be limited [31].

Accordingly, for women with preexisting AF (either paroxysmal or persistent) planning pregnancy, it is also crucial to assess if AF is related to structural heart disease; thus, thorough cardiac examination should be offered [4].

Management of atrial fibrillation during pregnancy

General recommendations

Maternal and fetal safety should be the first priority in the management of AF in pregnancy. Therapeutic approach in pregnant women with new-onset AF is generally based on the same principles that apply in nonpregnant women, but faster intervention may be necessary, even in the absence of underlying heart disease. Antiarrhythmic medications should be used cautiously to avoid harm to the fetus, since almost all of these drugs cross the placenta to a large extent [4]. Available relevant evidence from the literature is sparse for obvious reasons. Therefore, no firm recommendations can be made for administration of antiarrhythmic agents in AF during pregnancy, based only on pathophysiological considerations and data extracted from case reports.

In women with history of AF who are planning pregnancy, cardiovascular risk should be assessed. According to modified World Health Organization (mWHO) classification of maternal cardiovascular risk, which consists of five classes (with class IV corresponding to the highest risk), preexisting AF corresponds to class II risk. However, presence of structural heart disease may reclassify such women into higher risk levels [4]. Prepregnancy counseling is recommended, and patient should receive full information about associated maternal and fetal risks; estimated maternal cardiac event rate for mWHO class II risk is 5.7%−10.5% [4]. Lastly, close follow-up during pregnancy by an experienced cardiologist, obstetrician, and anesthesiologist is required, with at least one visit per trimester [4].

Rhythm control therapy—acute phase

Electrical cardioversion

Therapy should be urgent in situations that AF jeopardizes the safety of mother and fetus, resulting in diminished uterine blood flow and/or hemodynamic instability, i.e., in

cases of hypotension, pulmonary edema, angina, or syncope/presyncope. AF may not be well tolerated, especially in women with structural heart disease. According to current European Society of Cardiology (ESC) AF guidelines, direct electrical cardioversion is recommended whenever patient with ongoing AF is hemodynamically unstable and whenever the risk of ongoing AF for the mother or the fetus is considered high [1]. Several cases of successful cardioversion of maternal AF without harm to the fetus have been reported, [10,30].

Cardioversion should generally be preceded by anticoagulation, while use of intravenous (i.v.) β-blockers is recommended for initial rate control [1]. Energy requirements in pregnant and nonpregnant women are similar, and synchronized electrical cardioversion is effective in most cases, utilizing 50−100 J. Electrical cardioversion is generally considered safe in all trimesters of pregnancy [1]. The risk of inducing preterm labor, although present, seems acceptable, as it has been reported in 3 out of approximately 50 published cases [32,33]. Moreover, the risk of inducing fetal arrhythmias is limited since the amount of current that reaches the uterus is small and fibrillation threshold in fetuses of mammals is high [34]. In any case, the fetal heart rate should routinely be monitored during and after cardioversion, and if possible, facilities for emergency caesarean section should be available [1,32].

Besides AF, episodes of Afl may occur, particularly in patients with congenital heart disease. Atrial flutter is usually resistant to pharmacological cardioversion and poorly tolerated due to the increased ventricular response [4]. Therefore, electrical cardioversion should be also performed to restore sinus rhythm [4,35]; success rates in Afl have been reported to be up to 97% in nonpregnant populations [36].

Pharmacological cardioversion in patients without heart disease

Rhythm control is the preferred treatment strategy during pregnancy. Although no antiarrhythmic drug is completely safe, most of them are well tolerated and can be given with relatively low risk. Delivery of i.v. **ibutilide** may be considered for the termination of both Afl and AF in stable pregnant patients with structurally normal hearts [35,37−40]. Studies in nonpregnant populations reported that ibutilide achieved satisfactory conversion rates in AF/Afl of various duration intervals and was found to be superior compared with procainamide and sotalol [38−40]. Other data from nonpregnancy studies indicate that ibutilide has a conversion rate of up to 75%−80% in recent-onset AF and Afl [41]. In addition, Kockova et al. reported two cases of successful cardioversion of AF with ibutilide during pregnancy [37]. Therefore, this class III antiarrhythmic agent seems to be a good alternative to electrical cardioversion. Moreover, ibutilide pretreatment facilitates transthoracic defibrillation and decreases the energy requirement of electrical cardioversion. There is up to a 4% risk of Torsade de Pointes (TdP) and a 4.9% risk of monomorphic ventricular tachycardia. Hence, close monitoring in an intensive care unit setting is warranted during and at least for 4 h after drug infusion [37,41]. Data on the impact of ibutilide on fetal outcomes are scarce. At preclinical level, a dose equal to four times the proposed maximum clinical dose did not lead to teratogenicity in rats [42], whereas no adverse effects on the fetus were observed in human case reports [37].

Pharmacologic cardioversion with class Ic antiarrhythmic agents, such as **flecainide**, has also been used in pregnancy [43]. Interestingly, in a recent retrospective study, flecainide was found to be effective in conversion of fetal supraventricular tachycardia to sinus rhythm with a success rate of 78.6% when administered as monotherapy [44]. It has been suggested that rate-control drugs such as β-blockers should be administered along with class Ic antiarrhythmic drugs in Afl, because class Ic antiarrhythmic agents may slow the flutter rate and induce one-to-one atrioventricular (AV) conduction [45]. Evidence from human studies on the safety of flecainide for the fetus are lacking [4]. Fetal bradycardia and decreased heart rate variability have been reported [46]. Teratogenic effects have been observed in some, but not all, animal studies, mainly ossification disturbances [4]. Importantly, a recent metaanalysis showed similar rates of fetal loss with flecainide compared with digoxin [47], which is considered the safest antiarrhythmic drug [4].

As for class Ia antiarrhythmic agents, the more widely researched substance is **quinidine**, which is considered efficacious in pregnancy [48]. Although relevant data are limited, quinidine is considered relatively safe in pregnancy [49]. Thrombocytopenia, premature birth, and eighth cranial nerve damage have been reported as possible fetal side effects [4].

Pharmacological cardioversion in patients with heart disease

In pregnant women with structural heart disease and recent-onset AF, class I antiarrhythmic drugs and ibutilide should be avoided [1]. **Amiodarone** seems to be the only safe option for the mother to avoid malignant ventricular arrhythmias (i.e., TdP) that may occur with the use of other antiarrhythmic drugs [1]. However, amiodarone is a pharmaceutic agent for which there is evidence of human fetal risk, and its use in pregnancy is justified only if expected benefits outweigh risks [4]. Each 200-mg tablet contains 75 mg of iodine, and this additional iodine load may result in serious adverse effects for the fetus [49,50]. High rates of neonatal hypothyroidism (17%−23%), usually transient,

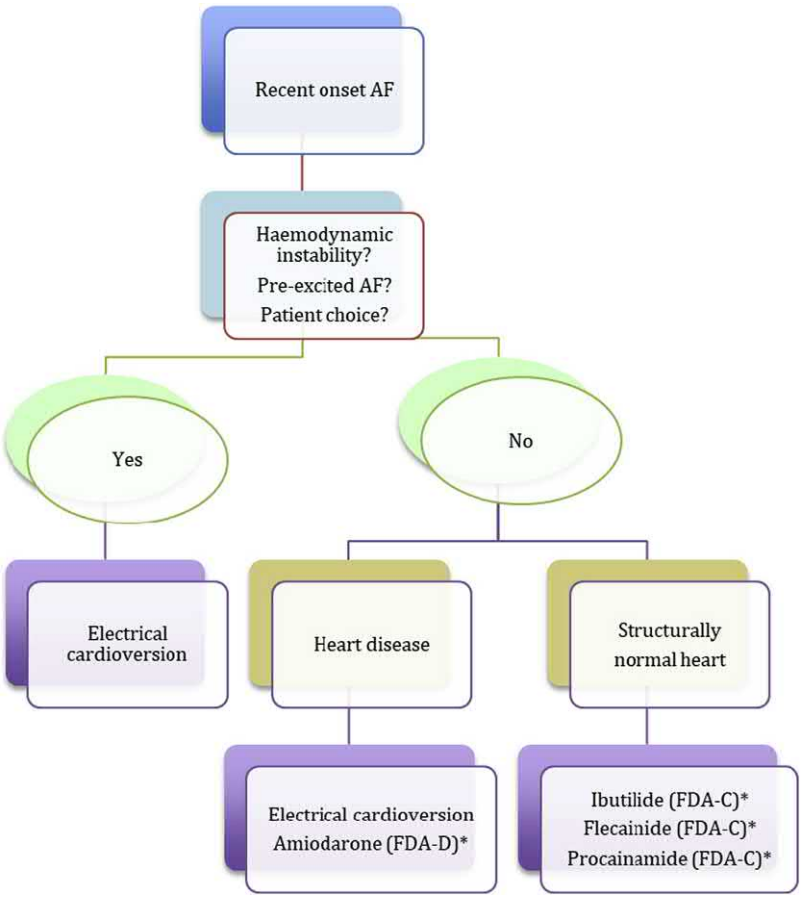

FIGURE 61.2 Rhythm control therapy of recent onset AF during pregnancy. *AF*, atrial fibrillation; *FDA*, food and drug administration. * *Refers to former FDA category.*

have been observed in pregnancies exposed to amiodarone [51,52]. Importantly, neurodevelopmental abnormalities, in presence of absence of hypothyroidism, have also been reported [51,52], whereas other possible side effects include goiter hyperthyroidism, bradycardia, delayed growth, and premature birth [4,46,49–52]. Therefore, amiodarone should also be avoided for acute restoration of sinus rhythm. For women with structural heart disease and recent-onset AF, **electrical cardioversion** is the safest treatment choice [4] (Fig. 61.2).

Rhythm control therapy—long term

A rhythm control strategy is generally preferred in pregnancy, and administration of a **cardioselective β-blocker** (metoprolol or bisoprolol) is the recommended first treatment option [4]. In case of symptomatic AF recurrence under β-blockade therapy, the decision to administer class I or III antiarrhythmic agents throughout pregnancy should take into account the presence of structural heart disease and potential adverse effects caused to the fetus by these drugs. In women without structural heart disease, **flecainide** and **sotalol** are considered effective in maintaining sinus rhythm [1,4]. Sotalol is generally considered safe in pregnancy [4], despite some data from animal studies indicating increased risk of fetal loss with high doses [53] and a human case where teratogenesis was reported [54]. Fetal bradycardia and hypoglycemia and slightly longer neonatal QTc interval are the most common adverse events observed [4,46,55]. Sotalol should not be used in patients with impaired systolic heart function or significant left ventricular hypertrophy [1]. In women with impaired systolic heart function, **amiodarone** seems to be the only effective option; however, as stated earlier, chronic administration is not safe [4,46,55], and in such cases, **rate control** strategies should generally be preferred. Amiodarone is to be used only as last choice agent in life-threatening conditions, i.e., in highly symptomatic recurrent AF where all other antiarrhythmic drugs have failed or are absolutely contraindicated [46] (Fig. 61.3).

Rate control therapy—acute phase, long term

In case that rate control is necessary, ESC guidelines favor the use of **β-blockers** (except atenolol) and/or **digoxin**. Digoxin has not been associated with teratogenic effects in

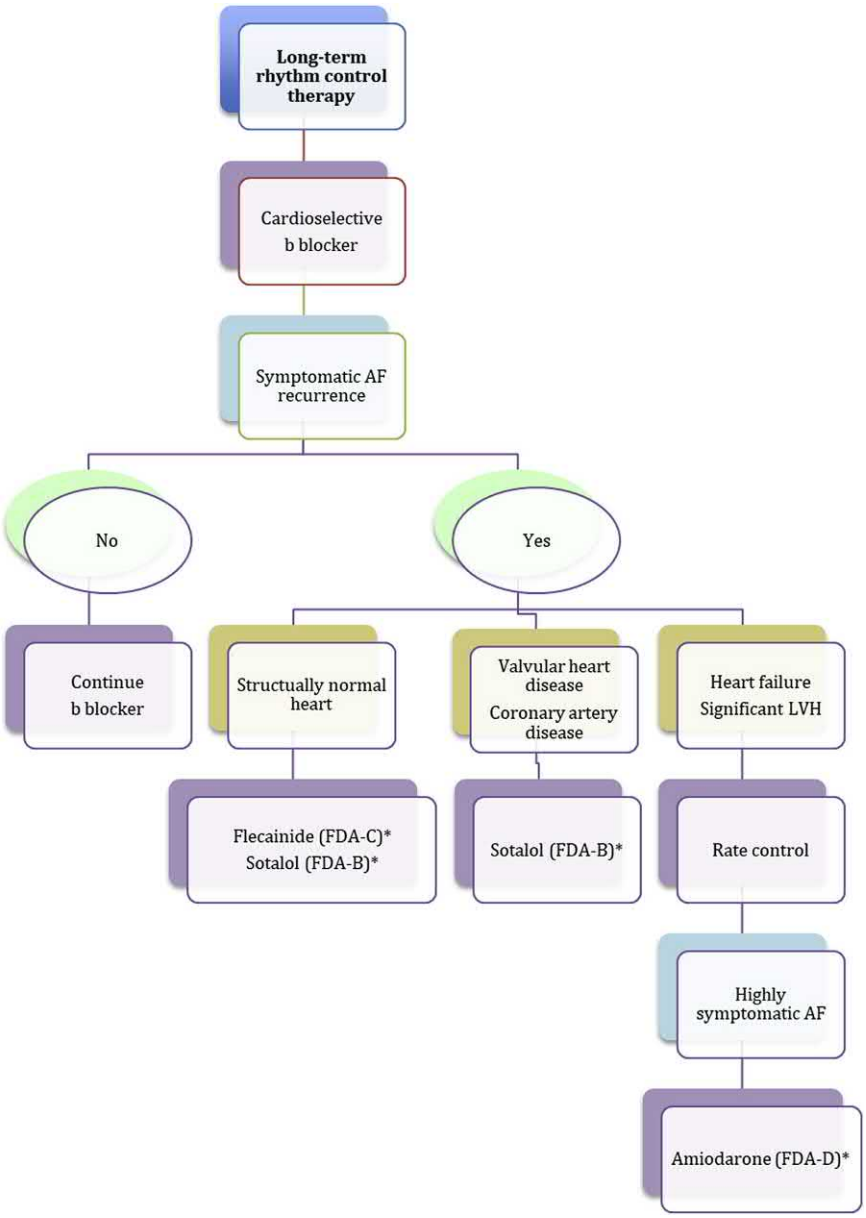

FIGURE 61.3 Long-term rhythm control therapy in AF during pregnancy. *AF*, atrial fibrillation; *LVH*, left ventricular hypertrophy; *FDA*, food and drug administration. * *Refers to former FDA category.*

humans or animals and is considered the safest antiarrhythmic agent in pregnancy [4]; however, fetal death has been reported in an extreme case of maternal intoxication, where a woman in the eighth month of pregnancy ingested 8.9 mg of digitoxin [56]. Of note, digoxin blood levels monitoring may be unreliable in pregnancy [4], because digoxin-like immunoreactive serum components, that is endogenous glycosides that react with antibodies against digoxin and are increased in pregnancy, can interfere with the radioassay used for determination of digoxin serum levels, resulting in falsely high measured concentrations [57–59].

β-Blockers are used in hypertensive pregnant women and are generally considered to be safe, with the exception of atenolol [1,4]. A metaanalysis reported increased risk for cardiovascular and neural tube congenital defects with β-blocker use in pregnancy [60]. However, a large European registry did not confirm these findings and suggested that β-blocker use was related only to multicystic renal dysplasia among other suspected congenital malformations, an association that was not significant for cardioselective β-blockers [61]. Nevertheless, β-blockers may be associated with several other adverse effects on the fetus, including intrauterine growth retardation, lower birth

weight, bradycardia, hypoglycemia, neonatal respiratory depression, and perinatal jaundice [4,60,62–66] with some evidence suggesting that side effects may be more pronounced if treatment is initiated early in pregnancy [67,68]. Consequently, β-blockers (except atenolol) can be administered during pregnancy, but it is recommended that they should be used with caution, at the lowest effective dose, and for the shortest time required [1].

Cardioselective β-blockers such as **metoprolol** and **bisoprolol** may be preferred to avoid β2-mediated peripheral vasodilation, increased uterine contractility, and fetal growth retardation [4,46]. Specifically, Tanaka et al. reported that metoprolol and bisoprolol were associated with lower rates of growth retardation compared with other β-blockers and similar rates compared with controls [68], whereas Duan et al. also recently observed that metoprolol use did not affect body weight compared with controls [65]. **Propranolol** is considered relatively safe in pregnancy. In women treated with propranolol for hypertensive pregnancy disorders, there were no congenital anomalies noted, but growth retardation (9%) has been reported [69]; it is unclear if this occurred due to the drug, hypertension alone, or their combination. Importantly, exposure to propranolol was not associated with increased risk for infants born small for gestational age in the recent large study by Duan et al. [65]. Atenolol is believed to cause higher rates of fetal growth retardation and is best avoided in pregnancy [4,65,67]. Reported rates of low birth weight (<2500 g) by Duan et al. were 18.0% with atenolol, 13.3% with metoprolol, and 7.6% with propranolol (5.2% for nonexposed controls), and among these agents, only atenolol exposure was associated with significantly higher risk of infants born small for gestational age compared with nonexposed controls [65].

Limited evidence exists for **nondihydropyridine calcium channel blockers** (verapamil and diltiazem) in pregnancy. Oral **verapamil** is believed to be safe and can be effective for rate control in AF; however, intravenous administration carries a risk of causing maternal hypotension and fetal hypoperfusion, bradycardia, and high-degree AV block [4,70]. **Diltiazem** has been linked to increased rates of fetal mortality, stillbirths, cleft palate, external malformations, skeletal, retinal, and heart abnormalities, and decreased fetal weight in animal studies; therefore, it should be used only if other treatment options are contraindicated [4,71,72].

Drug-specific recommendations

Apart from the potential detrimental effects of antiarrhythmic treatment for the fetus, the effect of these drugs on QT interval corrected for heart rate (QTc) is an important consideration when selecting antiarrhythmic drugs. Women present longer QTc interval compared with men, possibly due to actions of sex hormones, as testosterone is believed to shorten QTc interval, and although findings from studies are not consistent, estrogen may prolong QTc interval [73]. QT interval is further lengthened during pregnancy [74]. Moreover, women have a more than twofold greater risk of developing TdP induced by cardiovascular drugs compared with men [75]. Thus, close follow-up is required after administration of antiarrhythmic drugs known to prolong QTc interval, that is, class I and III agents [1].

Catheter ablation of atrial fibrillation/atrial flutter

Although catheter ablation is generally not recommended in AF patients during pregnancy, it should be considered prior to pregnancy to prevent AF recurrence. It also may be considered in patients with recurrent drug refractory and poorly tolerated AV nodal reentry tachycardia, AV reentrant tachycardia, focal ATs, cavotricuspid isthmus-dependent atrial flutter, and certain benign right-sided VTs [4]. In such cases, it should be postponed to the second trimester (if possible), until at least the completion of the period of major organogenesis, and should be performed by experienced operators with use of nonfluoroscopic echo- and electroanatomical mapping and catheter navigation systems [76].

The effects of radiation on the fetus depends on the radiation dose and the gestational age at which exposure occurs [23]. The International Commission on Radiological Protection recommends that the radiation dose for a pregnant worker in an electrophysiology laboratory should not exceed 1 mSv [77], while a conventional radiofrequency (RF) catheter ablation procedure in a pregnant patient exposes fetus approximately to 3 mSv [23].

There are few small studies and some case reports on catheter ablation during pregnancy using RF or cryoablation and three-dimensional mapping systems with no or minimum radiation exposure. They conclude that ablation can be safely and effectively performed without fluoroscopy in pregnant women with supraventricular arrhythmias (SVT). None of them, however, include AF or left AT ablation [22,78–82].

In nonpregnant patients with SVTs, recent publications confirm that RF or cryoablation combined with three-dimensional mapping systems is feasible and safe, reducing significantly the radiation exposure (Fig. 61.4) [83–85]. Sadek et al. performed 80 complex ablation procedures, of which 31 and 33 are with paroxysmal and persistent AF, respectively, using intracardiac echocardiography and a three-dimensional mapping system without fluoroscopy or lead protection. They conclude that nonfluoroscopic catheter ablation is feasible with no increase in procedural time [86]. Furthermore, recent metaanalysis and reviews have compared cryoballoon versus RF ablation in

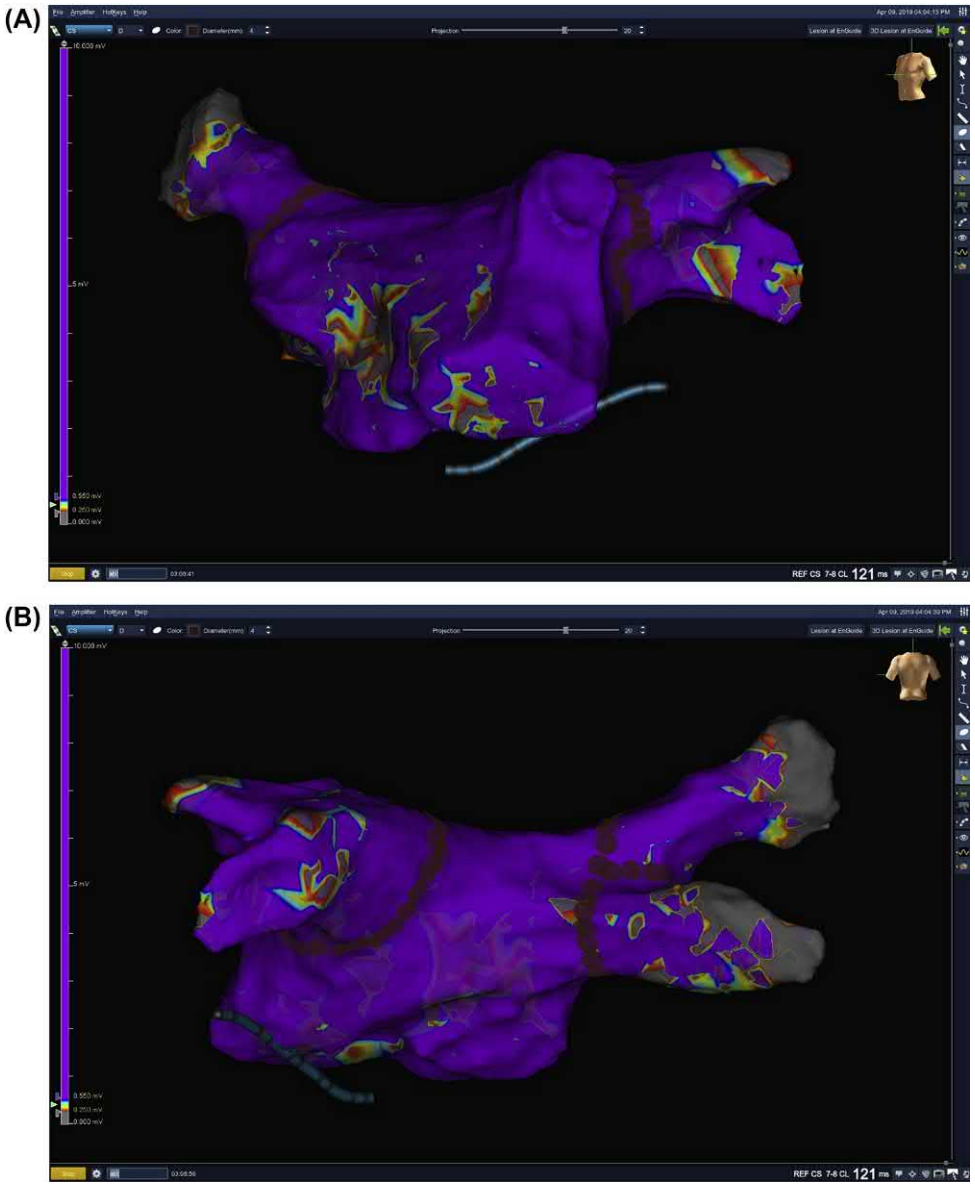

FIGURE 61.4 LA voltage mapping in a patient with PAF using EnSite-NavX system. Red dots represent the final circumferential ablation lesions around the left and right pulmonary veins in LAO and PA views. *LA*, left atrium; *AP*, anterior-posterior; *PAF*, paroxysmal atrial fibrillation; *LAO*, left anterior oblique; *PA*, posterior—anterior. Image courtesy of Department of Cardiology, Evangelismos General Hospital of Athens, Athens, Greece.

AF patients with similar results regarding the efficacy and safety profile, but with a markedly shorter procedure time with cryoablation [87—91]. Nonfluoroscopic cryo- and RF catheter ablation might have a role as a last resort in pregnant women with medically refractory and life-threatening arrhythmias, but more data are needed.

Anticoagulation management

The decision to initiate anticoagulation therapy in pregnant women with AF should be guided by assessment of risk for thromboembolic events, mainly strokes, with CHA_2DS_2-VASc score, i.e., similar to nonpregnant AF patients [1]. It should be emphasized, however, that tools currently used for prediction of stroke risk in the general AF population have not been validated in pregnancy. AF increases the risk for thromboembolism and stroke, whereas pregnancy itself is considered a hypercoagulable state [1,4]. However, the precise additive risk conferred by pregnancy in total thromboembolic risk in AF patients is not known. On the other hand, bleeding risk during pregnancy and peripartum period should be taken into account in the therapeutic management, since indirect data imply that necessity for anticoagulation is related to considerable maternal and fetal

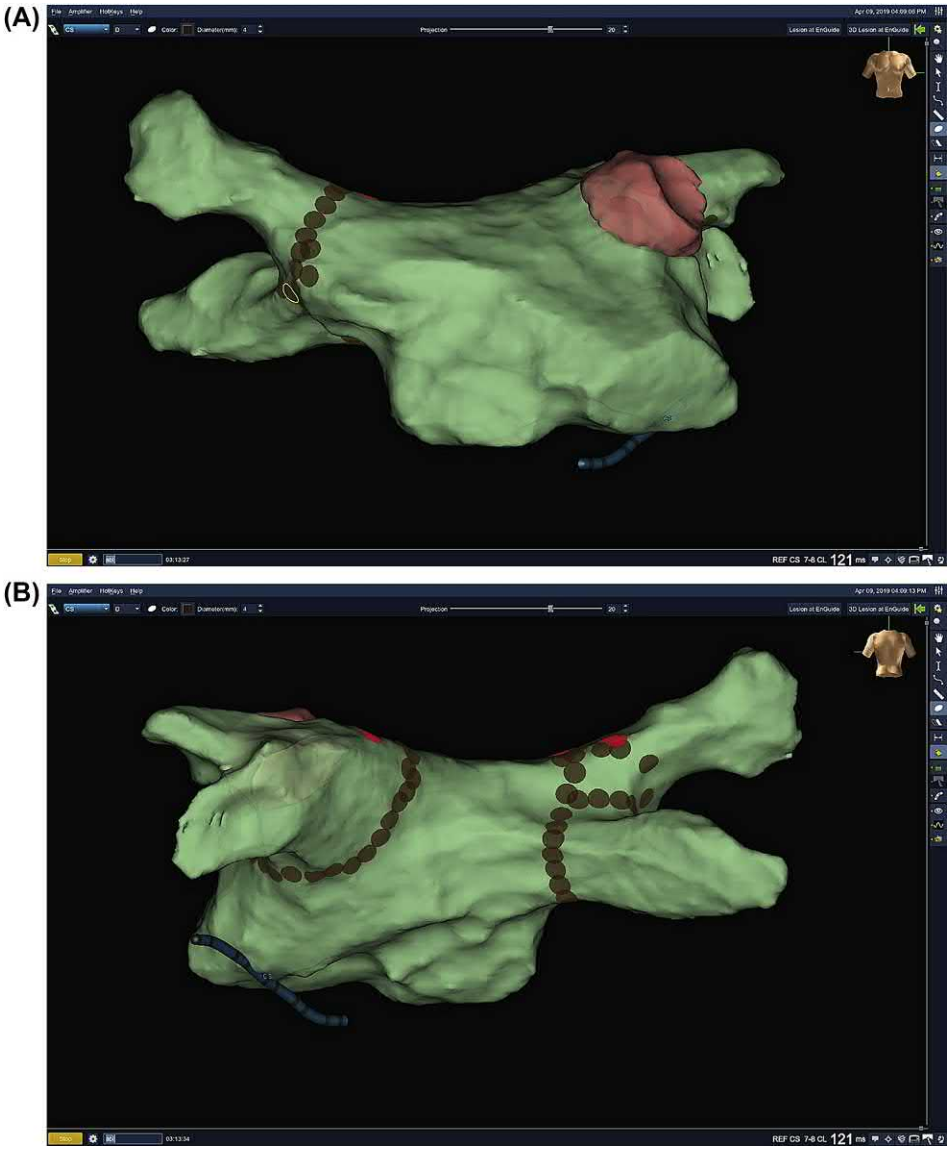

FIGURE 61.4 cont'd

morbidity [4,92]. Specifically, ROPAC investigators reported that pregnant women with a mechanical heart valve had increased odds for bleeding events and fetal miscarriage compared with pregnant women with tissue heart valves, while significantly fewer pregnancies in the mechanical valve group were free of serious complications [92].

Pregnant women are young, and in case of lone AF, they usually have a CHA_2DS_2-VASc score of 1 (due to female sex), i.e., anticoagulation is not required. In cases that AF is related to structural heart disease, CHA_2DS_2-VASc score may be higher (e.g., due to heart failure symptoms or impaired left ventricular ejection fraction), and if so, anticoagulation should be administered [1]. In addition, anticoagulation should be initiated in AF pregnant women with significant mitral valve stenosis (valve area$< 1.5\ cm^2$) or hypertrophic cardiomyopathy [4].

Immediate initiation of anticoagulation is important in all patients with AF duration less than 48 h scheduled for cardioversion, whereas long-term anticoagulation should be considered in those at risk of stroke. Patients with a CHA_2DS_2-VASc score of 1, who have been in AF for longer than 48 h, should start anticoagulation at least 3 weeks before cardioversion and continue it for 4 weeks afterward. Anticoagulation should be continued indefinitely in patients at risk of stroke. When early cardioversion is desired, trans-esophageal echocardiography (TOE) can exclude the majority of left atrial thrombi, allowing immediate cardioversion [1] (Fig. 61.5).

Vitamin K antagonists (VKAs) and heparin are the anticoagulant agents used in pregnancy [4]. Warfarin crosses the placenta, and the fetus may be "overdosed" even if the mother receives suboptimal dose [90]. Moreover, warfarin has been associated with significant side effects on the fetus, such as miscarriage and fetal loss,

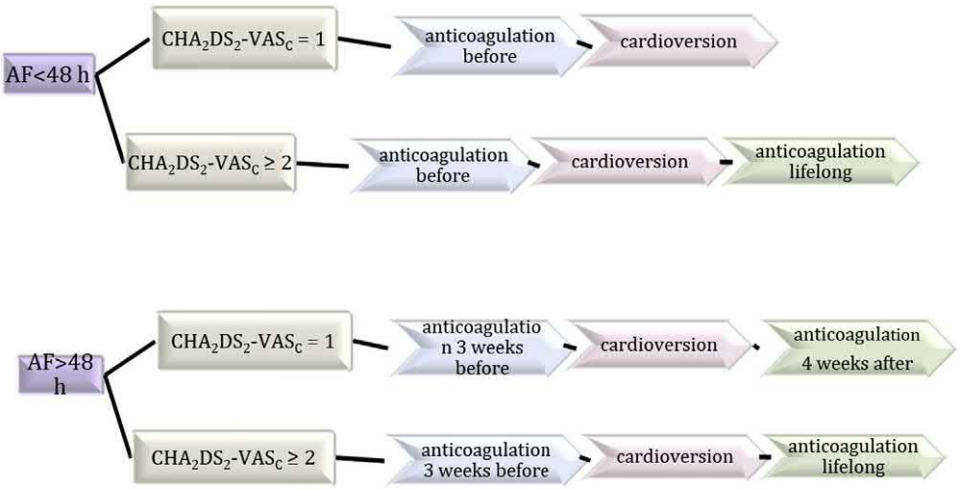

FIGURE 61.5 Long-term rhythm control therapy in AF during pregnancy. *AF*, atrial fibrillation; *LVH*, left ventricular hypertrophy; *FDA*, food and drug administration.

teratogenesis, mainly nasal hypoplasia and limb deficits, hemorrhage, and neurological and ocular abnormalities [92,94–99]. Rates of embryopathy can be up to 8%, and rates of miscarriage/fetal loss can be up to 35% [92,94,96,99]. Daily use of warfarin in dosage higher than 5 mg during the first trimester is considered responsible for a large proportion of these adverse effects [94,96,97,99,100]. Rates of embryopathy are low (~0.45% –0.9%) with warfarin daily dose lower than 5 mg [99,101], whereas VKA use during second and third trimester is associated with acceptable rates of fetopathy (~0.7%–2%) [4,95]. Furthermore, risk for miscarriage/fetal loss is lower (~13%–20%) with low-dose VKA [95,99,101] as well as with switch to heparin during gestation weeks 6–12 [92,95,99]. In addition, delivery while the mother being on VKA is associated with fetal intracranial bleeding; therefore, warfarin should be replaced by heparin at week 36 till labor [4,97]. Both low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) do not cross the placenta, thus presenting a favorable safety profile for the fetus compared with VKAs [95,99], whereas lower rate of miscarriage with LMWH use throughout pregnancy compared with sequential use of VKAs and LMWH has been reported in a recent metaanalysis [99]. Heparin-induced thrombocytopenia and osteoporosis seem to occur less frequently with LMWH than with UFH [102,103]; thus, longstanding use of UFH might best be avoided. On the other hand, the adequacy of anticoagulation provided by heparin in AF during pregnancy remains unproven. It is also unclear whether monitoring of anti-Xa factor levels, which is definitely recommended in pregnant women treated with LMWH due to presence of mechanical valve [4], is necessary for pregnant women with AF receiving LMWH.

Current recommendations suggest that, in pregnant women with AF necessitating anticoagulation, heparin, preferably LMWH, should be administered during the first trimester. During second and third trimester, either VKA or LMWH can be used; if VKA is chosen, switch to heparin is needed 2–4 weeks before labor (at approximately gestational week 36) [4] (Fig. 61.6). For pregnant women with mechanical valve (with or without AF), where adequate

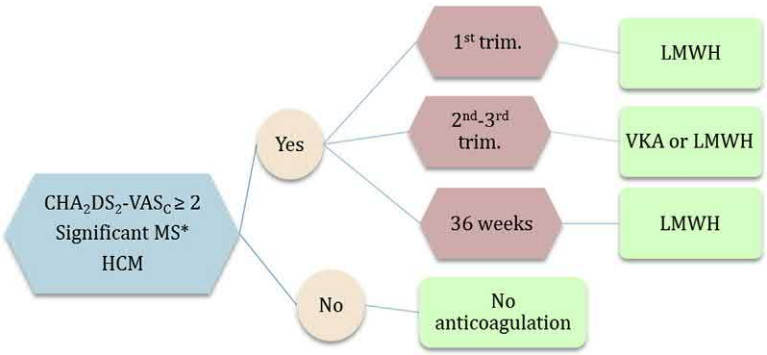

FIGURE 61.6 Anticoagulation in pregnant women with AF. *AF*, atrial fibrillation. *MS*, mitral stenosis; *HCM*, hypertrophic cardiomyopathy; *LMWH*, low molecular weight heparin; *VKA*, vitamin K antagonist. *Valve area < 1.5 cm^2.

anticoagulation is mandatory, VKA is recommended until week 36 if the required dose is relatively small (<5 mg for warfarin, <2 mg for acenocoumarol). If the usual VKA dose is higher, switch to LMVH or i.v. UFH for weeks 6–12 should be preferred with close monitoring of anti-Xa levels or activated partial thromboplastin time, respectively [4]. Other VKA or heparin regimens are believed to be less favorable but may be considered according to woman's preference after full information and consent. After week 36, VKA should be replaced by LMWH or i.v. UFH. If LMWH is preferred, i.v. UFH should be administered 36 h before planned delivery and discontinued 4–6 h before labor [4].

Non-VKA oral anticoagulants (OACs) are increasingly used in women of reproductive age for treatment and prevention of recurrence of pulmonary embolism and venous thromboembolism [104], and although contraindicated in pregnancy [4], they may accidentally be continued during the first weeks of gestation in women unaware of being pregnant. Potential consequences during pregnancy have not adequately been investigated, and experience is extremely limited. Preclinical studies did not provide evidence of teratogenicity [105]. Recently, an observational study assessed the outcomes of 37 pregnancies exposed to rivaroxaban, including 6-week follow-up of newborns [104]. Women were unaware of their pregnancies, and rivaroxaban was withdrawn after recognition of pregnancy, mainly during the first trimester. 6 spontaneous abortions, 8 elective terminations of pregnancy, and 23 live births were observed. Only one major malformation (conotruncal cardiac defect) was reported, which resulted in termination of pregnancy [104]. In addition, a systematic review examined 233 pregnancies exposed to non-VKA OACs, among which information on pregnancy outcome was available in 137 (58.8%) women [106]. In the latter population, rate of live births was 48.9%, miscarriage rate was 22.6%, and elective termination of pregnancy was performed in 28.5% of pregnancies. Reasons for elective termination were known only in one-third of cases and were not related to anticoagulant exposure. Anatomical abnormalities were observed in seven pregnancies (5.1%), and three of them (2.2%) were presumed to be drug related. Authors suggested that miscarriage rate was similar with that observed in the general population and malformation rate was possibly lower to corresponding rates reported with VKA exposure [106]. These data could at least reassure women exposed to non-VKA OACs early in pregnancy. However, no firm conclusions can be drawn, and non-VKA should be avoided in pregnancy until more evidence is available [4]. An overview of AF management during pregnancy is represented in Fig. 61.7.

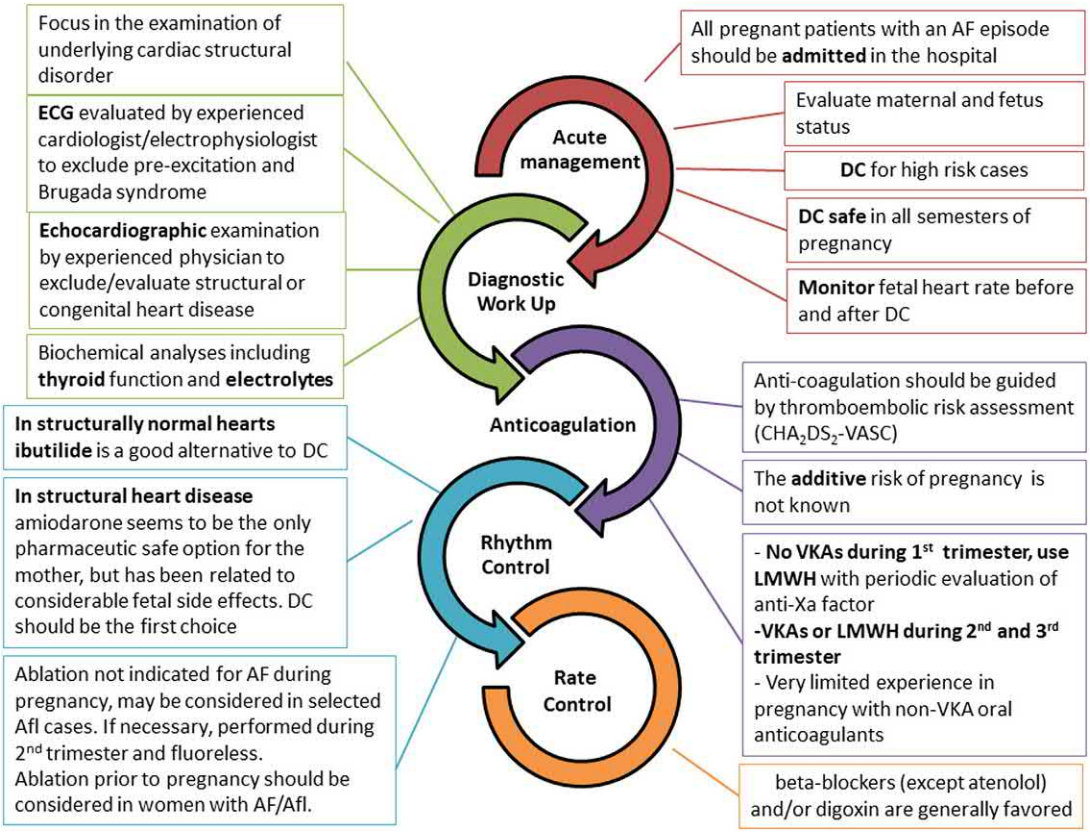

FIGURE 61.7 Overview of atrial fibrillation management during pregnancy. *AF*, atrial fibrillation; *Afl.* atrial flutter; *DC*, direct cardioversion; *ECG*, electrocardiogram; *LMWH*, Low molecular weight heparin; *VKAs*, vitamin K antagonists.

Conclusions

The incidence of new-onset AF in pregnancy is small but might disproportionally increase the morbidity of both mother and fetus. Accordingly, preexisting AF episodes may increase in intensity and frequency during pregnancy. As a general recommendation, we advise that pregnant women with AF should be evaluated by an experienced cardiologist or an electrophysiologist and treated as inpatients. In all cases, treatment options must be balanced in terms of expected benefit and potential harm and constantly updated according to mother's symptoms and fetus' signs. Given the older age of conception and increasing burden of risk factors in pregnant women, well-designed studies to assess optimal therapeutic management of complex arrhythmias in this population of special interest are highly anticipated.

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Chapter 62

Ventricular arrhythmias during pregnancy

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Introduction

An increased incidence of maternal cardiac arrhythmias is observed during pregnancy. While palpitations are common, life-threatening rhythm disorders are exceedingly rare in pregnancy, with prevalence of 2 in 100,000 hospital admissions [1]. Physiological changes that occur during pregnancy are potential factors that can promote arrhythmias, especially in females with underlying heart disease [1,2]. An increased number of women with known heart disease, especially women with congenital heart disease, are becoming pregnant as survival rates have been improved [3].

In all pregnant patients with ventricular arrhythmias, evaluation of the underlying etiology is essential. New-onset ventricular tachycardia (VT) is usually idiopathic and benign [5]. However, structural heart disease, inherited arrhythmogenic disorders, and cardiovascular disease should always be ruled out, as the risk of sudden cardiac death is higher. The prevalence of these disorders is 4.5−15.0 per 1000 pregnancies [5−7].

Moreover, diagnostic evaluation determines optimal therapeutic approach. The fetus may suffer both hemodynamic alterations during tachyarrhythmia and adverse effects of the medical treatment [5]. Therefore, symptoms especially of hemodynamic instability and underlying heart disease and embryonic age are factors that should be evaluated before medical treatment.

Mechanisms of ventricular arrhythmias in pregnancy

Pregnancy is associated with significant physiological changes in the cardiovascular system in response to increased metabolic demands and to obtain adequate uteroplacental circulation [8]. Plasma volume is expanded by 40%−50% above baseline at 32 weeks of gestation, and a similar increase in cardiac output is observed [5]. After the first-half of pregnancy, the increase in cardiac output is achieved by a gradual increase in heart rate. The overall change in heart rate represents a 20%−25% increase over baseline, reaching a maximum in the third trimester [8].

In case of preexisting heart rhythm disorders, exacerbation of arrhythmia during pregnancy is common [1]. The aforementioned adaptive mechanisms could be related to the appearance of ventricular arrhythmias during pregnancy. Mechanical stretch has been shown to prolong action potential duration and produce early afterdepolarizations in ventricular myocytes [9]. High resting heart rate has also been demonstrated to be associated with ventricular arrhythmogenesis [10]. Moreover, pregnancy alters cardiovascular and sympathetic nervous system responses to physiologic stimuli and can aggravate ventricular arrhythmias [11].

Ventricular arrhythmias in pregnant women without structural heart disease

Idiopathic VT in patients without structural heart disease, inherited primary arrhythmia syndromes, or metabolic/electrolyte abnormalities is a distinct entity. Various subtypes of idiopathic VT have been recognized and classified according to the site of origin, the clinical phenotype (repetitive monomorphic ventricular contractions, nonsustained monomorphic VT, or exercise-induced sustained VT), and the underlying mechanism (triggered activity mediated by catecholamine-induced delayed afterdepolarizations or intrafascicular/interfascicular reentry) [12]. The most common form of idiopathic ventricular arrhythmias is an outflow tract VT, which usually originates from the right ventricular outflow tract. Palpitations, fatigue, and lightheadedness are the most common symptoms, whereas syncope is rare. The prognosis of these patients is excellent, and the risk of sudden cardiac death is insignificant.

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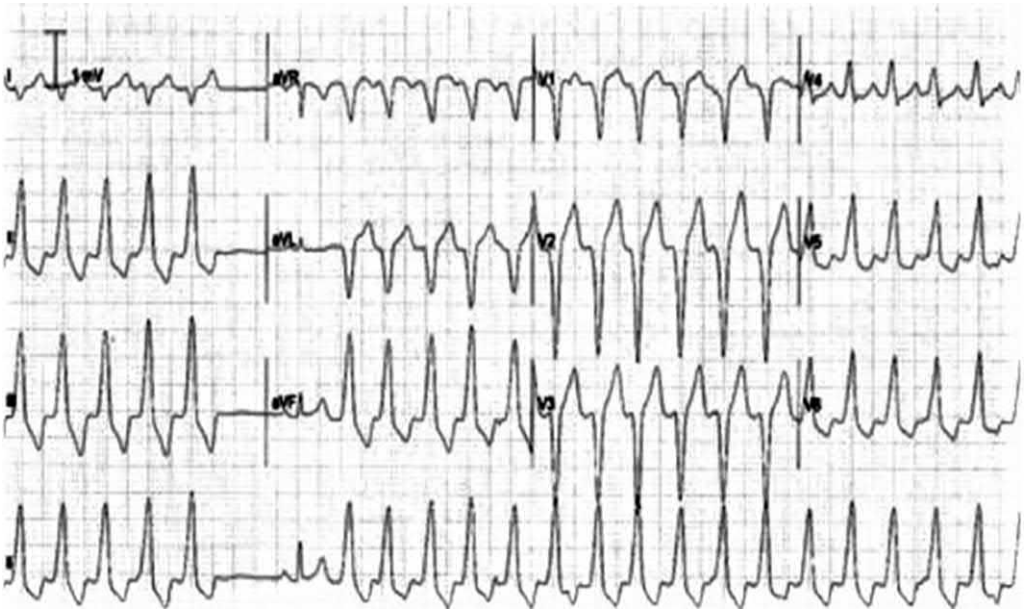

FIGURE 62.1 12-lead ECG of a 36-year-old pregnant woman admitted with a 4-week history of increasingly intrusive palpitations associated with presyncope. Bursts of broad complex tachycardia are seen with a left bundle branch block morphology, and precordial transition at V4 consistent with origin from the right ventricular outflow tract. *From Hogarth AJ, Graham LN. Normal heart ventricular tachycardia associated with pregnancy: successful treatment with catheter ablation. Indian Pacing Electrophysiol J March 12, 2014;14(2):79–82 with permission.*

The mean age at diagnosis of idiopathic outflow tract tachycardias is 50 ± 15 years with a range that includes women of childbearing age [13]. Shotan et al. assessed the relationship between symptoms and cardiac arrhythmias in 110 pregnant patients without evidence of structural heart disease who were referred for evaluation of palpitations, dizziness, and syncope [14]. These patients were compared with 52 consecutive pregnant patients referred for evaluation of an asymptomatic functional precordial murmur. Both groups had a high incidence of arrhythmias on Holter monitoring with isolated ventricular premature beats of 59% in the study group and 50% in the control group, whereas the incidence of multifocal PVCs was higher in the study group (12%) than in the control group (2%, $P < .05$). A substantial reduction of premature ventricular beats was observed postpartum, whereas VT or ventricular fibrillation was not documented in any of the patients.

Nakagawa et al. studied 11 pregnant woman who presented new-onset ventricular arrhythmias during pregnancy [15]. Ventricular arrhythmias had characteristics similar to those of idiopathic VT, most frequently of right outflow tract origin. The onset of the first episode was distributed equally over the three trimesters. The frequency of the premature ventricular contractions decreased more than 95% in 83% of the patients, whereas couplets and VTs disappeared completely in all patients after delivery. Hormonal variation has been associated with the burden of VT originating from the right outflow tract.

The aforementioned studies confirm the relationship between ventricular arrhythmias and pregnancy as well as their benign prognosis in patients without structural defects. However, it is crucial to rule out cardiomyopathies, especially arrhythmogenic right ventricular cardiomyopathy, which may be associated with malignant ventricular arrhythmias originating from the outflow tract [12]. Therefore, careful clinical, electrocardiographic, and echocardiographic assessment is important to identify those individuals with structural heart disease. Fig. 62.1 presents a typical case.

Ventricular arrhythmias in pregnant women with structural heart disease

Pregnant women with structural heart disease are in increased risk of presenting ventricular arrhythmias during pregnancy [5]. In contrast to pregnant patients with normal left ventricular function, there is a poor prognosis when VT is associated with structural heart disease. In the European Registry on Pregnancy and Heart disease that was initiated in 2007 by the European Society of Cardiology, congenital heart disease was the largest subgroup (66%) [16]. As a result of improvements in long-term outcome, increasing numbers of women with congenital heart disease are becoming pregnant [17]. Not only the underlying congenital substrate of the heart defects but also ventricular incisions and prosthetic materials after surgical and interventional treatment predispose to monomorphic VTs of reentrant mechanism [3]. Additionally, myocardial fibrosis and disarray may also lead to development of polymorphic VT and ventricular fibrillation [3]. In a study of 28 female patients with repaired congenital heart disease,

a significantly higher incidence of tachyarrhythmia during pregnancy and in the postpartum period was demonstrated compared with controls [18]. The type of arrhythmia presents remarkable differences among the types of congenital heart disease. Monomorphic VTs comprise more than 80% of all ventricular arrhythmias in Tetralogy of Fallot. In contrast, less than half of all ventricular arrhythmias in dextro-Transposition of the great arteries are monomorphic VT, and the remaining are polymorphic VT and ventricular fibrillation [3].

Importantly, the majority of the patients with congenital heart disease are diagnosed and treated long before pregnancy [16]. Therefore, awareness of the maternal and fetal risk in this population supports optimal care and prepregnancy counseling. This could contribute to the relatively favorable outcomes compared with other structural heart diseases, especially in developed countries. In the aforementioned European Registry, significantly lower incidence of ventricular arrhythmias was also reported in pregnant women with congenital heart disease compared with those with cardiomyopathies (1.6% vs. 11%; $P < .001$).

The prevalence of cardiomyopathies in women of childbearing age is uncommon [19]. However, pregnancy in women with cardiomyopathies is associated with significant cardiac and neonatal complications. Hemodynamic changes that occur during pregnancy can decompensate even previously asymptomatic women. The presence of cardiac arrhythmias has also been demonstrated to predict outcome [19].

VT may manifest any time during pregnancy. In the Registry Of Pregnancy And Cardiac disease (ROPAC), ventricular arrhythmias occurred in 1.4% of pregnant women with cardiovascular disease, mainly in the third trimester [20]. In patients who present with new-onset VT in the past few weeks of pregnancy or within 6 months of the delivery, a possibility of peripartum cardiomyopathy should be considered [5].

Peripartum cardiomyopathy is defined as an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction toward the end of pregnancy or in the months following delivery, where no other cause of heart failure is found [5]. It is a diagnosis of exclusion. The left ventricle may not be dilated, but the ejection fraction is nearly always reduced below 45% [21]. The incidence varies from 1:300 to 1:4000 pregnancies. Although the most frequent initial presentation is symptoms of heart failure, some patients may present with complex ventricular arrhythmias (Fig. 62.2) [21]. Therefore, peripartum cardiomyopathy should always be ruled out in women presenting with new-onset VT during the past 6 weeks of pregnancy or in the early postpartum period.

In female patients with arrhythmogenic right ventricular cardiomyopathy, 3%−13% of pregnancies have been reported to be complicated by ventricular arrhythmias [22,23]. However, VT incidence is not significantly increased during pregnancy, and risk stratification based on prior events may not be accurate.

Ischemic cardiomyopathy is uncommon in women of childbearing age, but myocardial infarction complicated by ventricular arrhythmias with or without (coronary dissection, spasm) coronary artery disease has been observed during pregnancy [24].

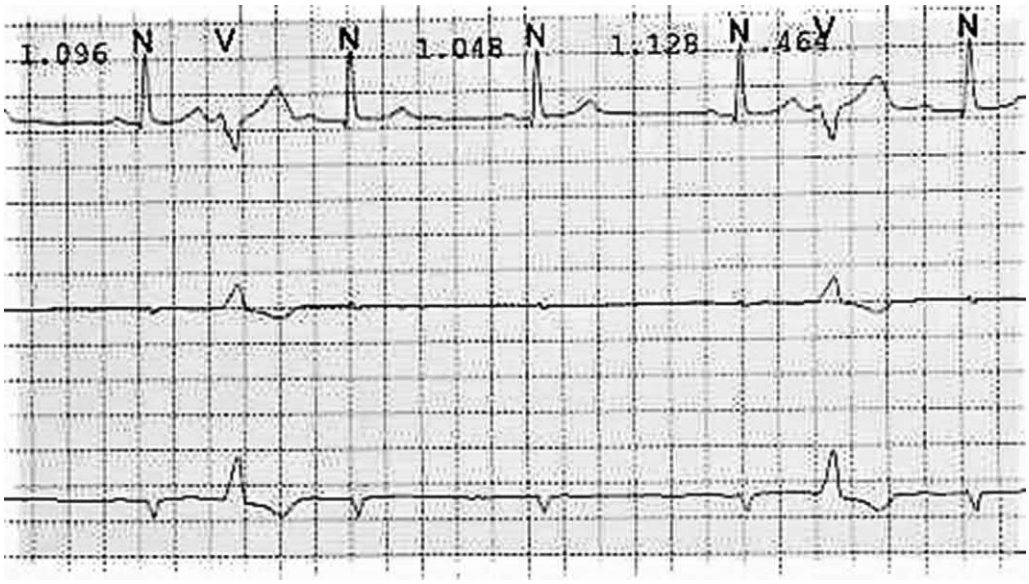

FIGURE 62.2 Ventricular quadrigeminy in 38-year-old woman with peripartum cardiomyopathy.

Inherited primary arrhythmia syndromes

Congenital long QT syndrome is a hereditary disorder of cardiac ion channels, characterized by QT prolongation and T-wave abnormalities on the ECG that are associated with polymorphic ventricular tachyarrhythmias, typically the torsade de pointes. The usual age range of events differs for each genotype. Importantly, although cardiac events are more common before age 40 years for all subtypes, this risk has been shown to be reduced during pregnancy [25]. The hyperestrogenic state may be a factor associated with a reduced risk of cardiac events during this time period. On the contrary, an increased risk during the postpartum period has been identified when compared with the preconception time period [25,26]. This risk has been demonstrated as significant only among probands with the long QT syndrome but not among first-degree relatives [26].

Catecholaminergic polymorphic VT is characterized by life-threatening arrhythmias during exertion or emotional stress (Fig. 62.3). The arrhythmic risk in catecholaminergic polymorphic VT patients has not found to be elevated compared with the nonpregnant period [27].

Women with Brugada syndrome can have a safe pregnancy and peripartum period [28,29]. In a retrospective, single-center study, serious events were not more frequent during pregnancy and the peripartum period in women with Brugada syndrome. Moreover, the occurrence of syncope during pregnancy was not associated with a worse outcome in the peri- and postpartum periods or during follow-up [28].

Treatment

In general, management of ventricular arrhythmias in pregnancy is similar to that in nonpregnant patients. In case of benign arrhythmias, as premature ventricular beats, in patients without structural heart disease and asymptomatic or minimally symptomatic, reassurance and avoidance of stimulants such as caffeine, smoking, and alcohol are adequate [30]. In the majority of cases of low-risk patients, the burden of arrhythmia is reduced spontaneously after labor [6].

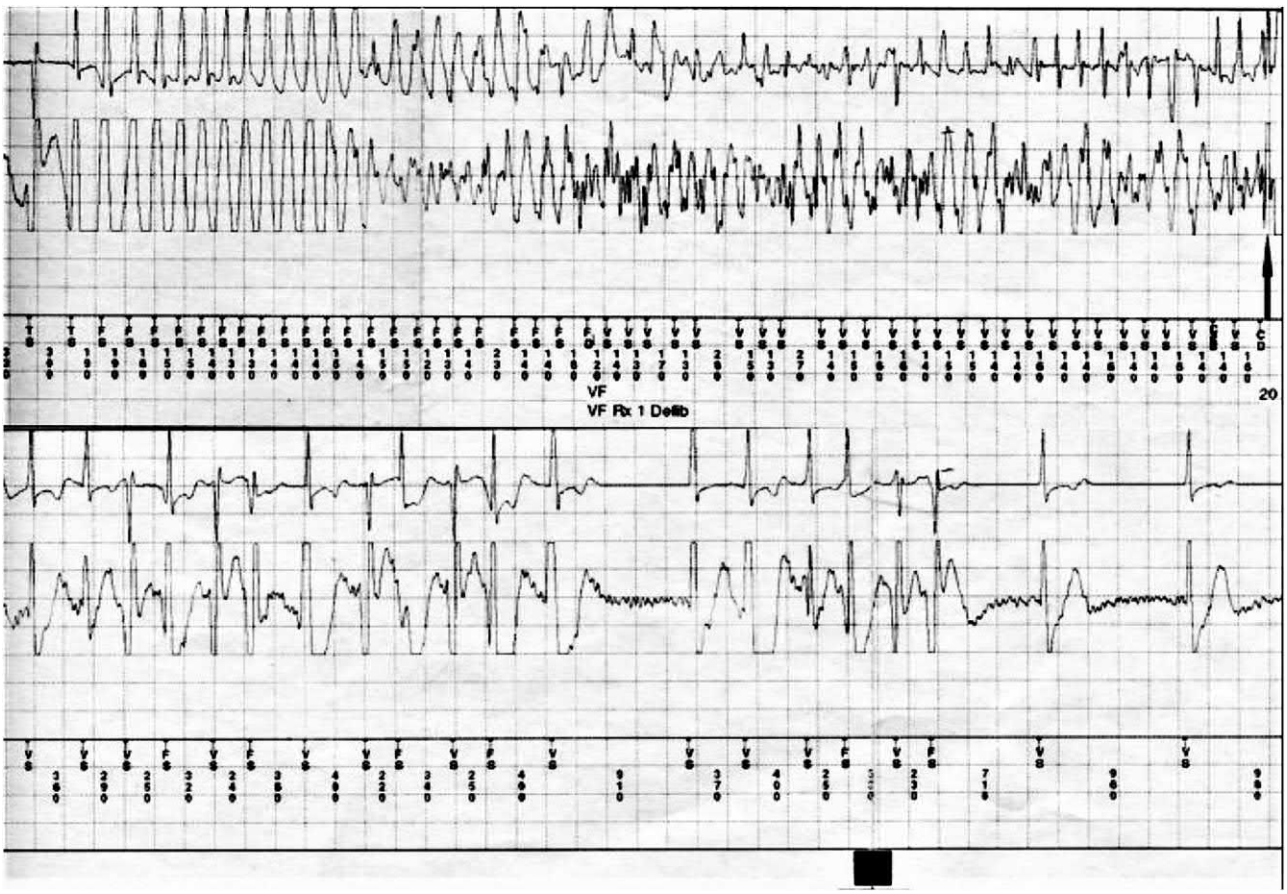

FIGURE 62.3 ECG lead showing a ventricular fibrillation event in a teenage pregnancy with catecholaminergic polymorphic ventricular tachycardia. Failure of antitachycardia pacing was followed by degeneration into ventricular fibrillation and ICD therapy (*arrow*). Erratic rhythm with bursts of ventricular tachycardia continued after the ICD therapy before spontaneously reverting to normal sinus rhythm. *ICD*, implantable cardioverter defibrillator. *From Ahmed A, Phillips JR. Teenage pregnancy with catecholaminergic polymorphic ventricular tachycardia and documented ICD discharges. Clin Case Rep March 2, 2016;4(4):361–5 with permission.*

Antiarrhythmic drugs

Pharmacological treatment is complicated because of the risk of teratogenic effects of drugs on the fetus. This risk is greater between the first and eighth week of pregnancy [5]. For this reason, drugs should be reserved for arrhythmias that cause significant symptoms or are life-threatening to the mother or fetus. If long-term drug treatment is recommended, it is advised to begin as late in pregnancy as possible and to use the lowest effective dose [5]. Importantly, risk of teratogenicity is based on epidemiological studies, published case reports, and animal studies rather than on controlled clinical trials.

In 1979, the Food and Drug Administration (FDA) introduced a classification to denote the safety of drugs for use among pregnant women [31]. The followed five categories have been defined using the letters A to D, together with an X category, to determine the teratogenic risk of drugs and their effect on fetal growth and development:

A: controlled studies show no risk.
B: chance of fetal harm is remote.
C: potential benefits outweigh the risk.
D: positive evidence of risk.
X: contraindicated.

The classification of the antiarrhythmic drugs is presented in Table 62.1.

Most of antiarrhythmic drugs are FDA category C, meaning that risk to the fetus cannot be ruled out. As of 2015, the FDA discontinued the pregnancy risk categories. The ABCDX system has been replaced by the FDA Pregnancy and Lactation Labeling Rule (PLLR) that provides a descriptive risk summary and detailed information on animal and clinical data [5]. In the absence of adequate human safety data, decision-making should be based on individual drug efficacy and safety profiles, and the available animal data, and the decision must be made together with the patient [5]. Pregnancy-related adverse effects associated with antiarrhythmic drugs are presented in Table 62.2.

TABLE 62.1 FDA classification of antiarrhythmic drugs used for ventricular arrhythmias.

FDA category	Antiarrhythmic drug
A	No antiarrhythmic drug
B	Sotalol
C	Procainamide, quinidine, disopyramide, lidocaine, mexiletine, flecainide, propafenone, metoprolol, propranolol, bisoprolol, labetalol, verapamil, diltiazem, adenosine
D	Amiodarone, atenolol, phenytoin
X	No antiarrhythmic drug
-	Ajmaline

TABLE 62.2 Reported fetal adverse effects of antiarrhythmic drugs in pregnancy.

Adenosine	**No adverse effects reported**
Amiodarone	Thyroid insufficiency, hyperthyroidism, goiter, bradycardia, growth retardation, premature birth
Beta-blockers	Growth retardation, bradycardia, hypoglycemia, uterine contractions, hyperbilirubinemia (hypospadias and birth defects have been reported for atenolol)
Diltiazem	Possible birth defects (animal data with skeleton, heart, retina, and tongue abnormalities)
Disopyramide	Uterine contractions
Flecainide	Inadequate human data (contradictory animal data of teratogenic effects)
Lidocaine	Bradycardia, acidosis, central nervous system toxicity
Mexiletine	Bradycardia (inadequate human data)
Procainamide	Limited experience
Quinidine	Thrombocytopenia, premature birth, eighth cranial nerve toxicity
Sotalol	Bradycardia, hypoglycemia
Verapamil	Greater risk of hypotension in IV administration

Management of specific arrhythmias in pregnancy

Idiopathic ventricular tachycardia

In patients with idiopathic VT, identification of the location of origin of tachycardia defines the choice of medical treatment. The more common idiopathic VT originating from the right ventricular outflow tract is associated with a characteristic ECG morphology of LBBB with inferior axis (Fig. 62.1), whereas left ventricular outflow tract VT is suggested by LBBB morphology with inferior axis with small R waves in V1 and early precordial transition (R/S = 1 by V2 or V3) or RBBB morphology with inferior axis and presence of S wave in V6 [12].

The initial drug of choice for outflow tract VT is usually a β-blocker [5,12]. β-Blockers are generally safe during pregnancy. Maternal use of β-blockers in the first trimester was not associated with a large increase in the risk for congenital malformations in a recently published international cohort study [32]. However, restriction of intrauterine growth has been reported [1]. As β2-blockade reduces

umbilical flow and increases uterine contractility, β1-selective blockers might be preferable. Calcium channel blockers should also be considered. Verapamil is the preferred calcium antagonist during pregnancy, as no evidence of teratogenicity or severe adverse effects has been reported [1]. In the contrary, one retrospective analysis of 27 newborns exposed during the first trimester to diltiazem suggests an association with birth defects [33]. Sotalol or class IC agents may be considered if other agents are ineffective [30]. Acute termination of outflow tract VT can be achieved by vagal maneuver or adenosine (6–24 mg), whereas intravenous verapamil (10 mg given over 1 min) can be given if the patient has adequate blood pressure [12].

Idiopathic fascicular VT has a characteristic ECG morphology of RBBB with left superior axis (exit posterior fascicle) or right inferior axis (exit anterior fascicle) and is verapamil sensitive [12].

Idiopathic VT that causes severe symptoms or cardiomyopathy should be treated by catheter ablation before pregnancy, if the pregnancy was previously planned [5,30]. Fig. 62.4 presents the management algorithm of idiopathic ventricular arrhythmias in pregnancy.

Ventricular tachycardia in patients with structural heart disease

In pregnant women with VT associated with structural heart disease, risk of sudden death is higher [5,19]. The management is different compared with idiopathic VT and depends on the degree of hemodynamic instability.

Sotalol or procainamide intravenously should be considered for acute pharmacological conversion of hemodynamically stable monomorphic sustained VT [5]. Sotalol is classified as a category B drug with available human safety data [34,35]. Moreover, animal studies have failed to show teratogenicity, although sotalol crosses the placenta. However, some cases of neonatal bradycardia have been reported. Intravenous sotalol reaches therapeutic levels within minutes, and the corresponding dose is slightly less than oral dose [34,35]. Procainamide has not been associated with teratotoxicity even when used during the first trimester of pregnancy (FDA category C), although experience is limited [1,5]. Procainamide doses have varied in the literature, ranging between "at least" 500 mg and "up to" 17 mg/kg. Infusion should be performed slowly over 25–30 min, while administration can be repeated after 5 min.

Lidocaine has also been proposed for first-line therapy in pregnancy. However, administration of lidocaine during fetal acidosis can cause heart and central nervous system toxicity in the newborn and, therefore, should be avoided in prolonged labor, fetal acidosis, and maternal liver or heart failure [1,35]. In addition, intravenous lidocaine is only moderately effective in patients presenting with monomorphic VT [30].

Intravenous amiodarone is not ideal for early conversion of stable monomorphic VT [5]. Amiodarone use during pregnancy has been associated with fetal goiter, neonatal hypothyroidism, growth retardation, and premature delivery [35]. Its use should be avoided during pregnancy apart from acute conversion of sustained, monomorphic VT that is hemodynamically unstable, refractory to electrical cardioversion, or not responding to other drugs [5]. The management algorithm of VT in pregnant women with structural heart disease is presented in Fig. 62.5.

Electrical cardioversion

For acute treatment of VT with hemodynamic instability, immediate cardioversion is recommended [5]. Direct current cardioversion is safe at all stages of pregnancy, and the risk of inducing fetal arrhythmias is small, because the current reaching the fetus is insignificant [36]. Even if VT is well tolerated, electrical cardioversion can be the initial approach, as timely restoration of sinus rhythm is desirable [5].

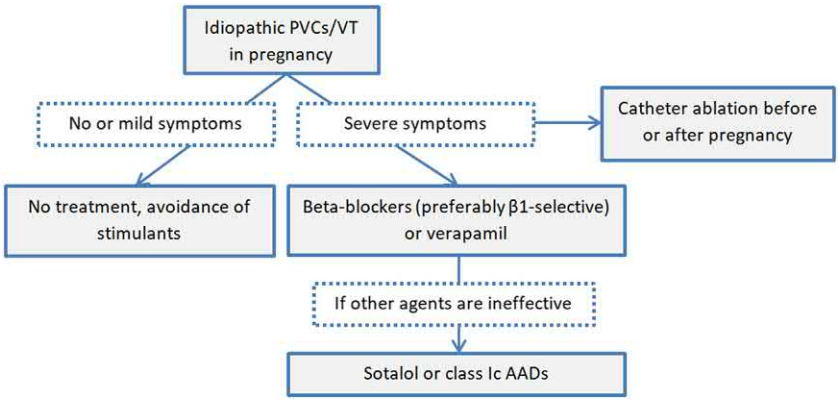

FIGURE 62.4 The management algorithm of idiopathic ventricular arrhythmias in pregnancy. *AADs*, antiarrhythmic drugs; *PVCs*, premature ventricular contractions; *VT*, ventricular tachycardia.

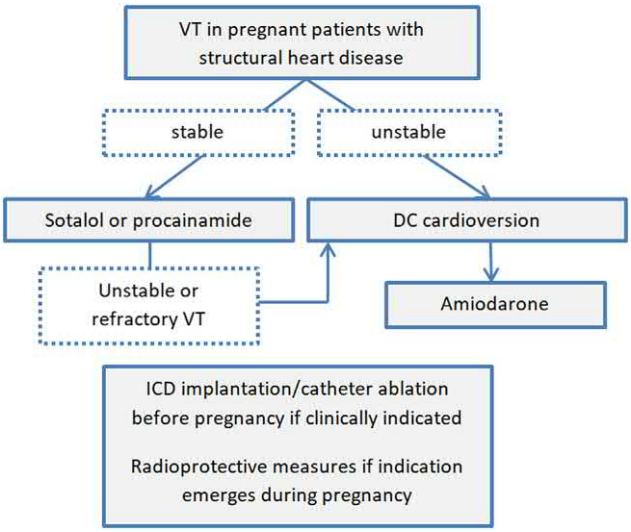

FIGURE 62.5 The management algorithm of ventricular tachycardia in pregnant women with structural heart disease. *ICD*, implantable cardioverter defibrillator; *VT*, ventricular tachycardia.

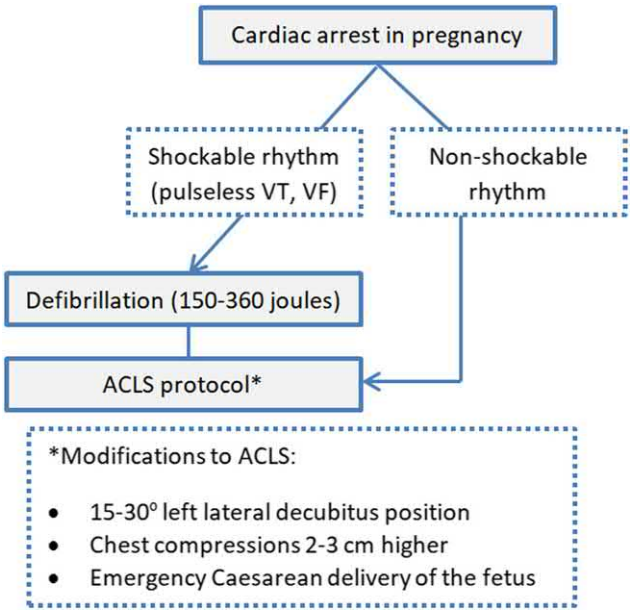

FIGURE 62.6 The management algorithm of cardiac arrest in pregnancy. *ACLS*, advanced cardiac life support; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia.

Cardiac arrest in pregnancy

Resuscitation guidelines for pregnancy are based mainly on case series, extrapolation of data of nonpregnant cardiac arrests, studies using mannequin models and expert opinion based on the physiology of pregnancy, and changes that occur in normal labor [36]. Fetal survival usually depends on maternal survival.

For the pregnant women presenting with cardiac arrest and a shockable rhythm (pulseless VT or ventricular fibrillation), external defibrillation should be followed as for any other patient [36]. Physiological changes during pregnancy, as expansion of thoracic and pulmonary blood volume, increase of end-diastolic volume, and undergone mild ventricular hypertrophy and dilation, do not affect transthoracic impedance [37]. Therefore, current energy requirements for adult defibrillation are appropriate for use during pregnancy. For biphasic waveforms, initial shock energy of at least 150 J is recommended. With manual defibrillators, it is appropriate to consider escalating the shock energy if feasible, after a failed shock or recurrence of a shockable rhythm (150–360 J) [36].

Interventions as maintenance of the airway and ventilation, administration of adrenaline, and identification and correction of reversible causes are common to both pregnant and nonpregnant patients. On the other hand, some modifications to basic life support are recommended for pregnant victims of cardiac arrest after the 20th week of gestation [36,38]. The compression of the uterus on the inferior vena cava and aorta can affect venous return and cardiac output in the supine position. Placing the patient in 15–30 degrees of left lateral decubitus position has been shown to shift the gravid uterus and relieve aortocaval compression. Manual left uterine displacement is also recommended if the uterus is palpable or visible at or above the umbilicus [36,38]. Moreover, the gravid uterus may displace the contents of the thorax, resulting in a cephalad anatomic shift in late pregnancy. For third trimester patients, hand placement is recommended to be 2–3 cm higher on the sternum than in nonpregnant individuals, although this recommendation is based on expert consensus only [36,38]. Emergency caesarean section should also be performed if initial resuscitation efforts fail [36]. The management algorithm of cardiac arrest in pregnancy is presented in Fig. 62.6.

Implantable cardioverter defibrillators and pregnancy

Natale et al. performed a multicenter retrospective analysis of 44 pregnant women with implantable cardioverter defibrillators (ICDs) and found that the majority completed and tolerated pregnancy without serious complications [39]. During pregnancy, 11 women received at least one ICD shock. In a smaller subsequent study, pregnancy also did not increase the risk of an ICD-related complication under appropriate management [40]. In general, ICD shocks have not been reported to cause maternal or fetal effects. Fig. 62.7 presents an uncomplicated pregnancy in a woman with hypertrophic cardiomyopathy.

Importantly, in this series of Natale et al., only 2 of 44 women had the ICD implanted while pregnant. If clinically indicated, implantation of ICD is recommended before

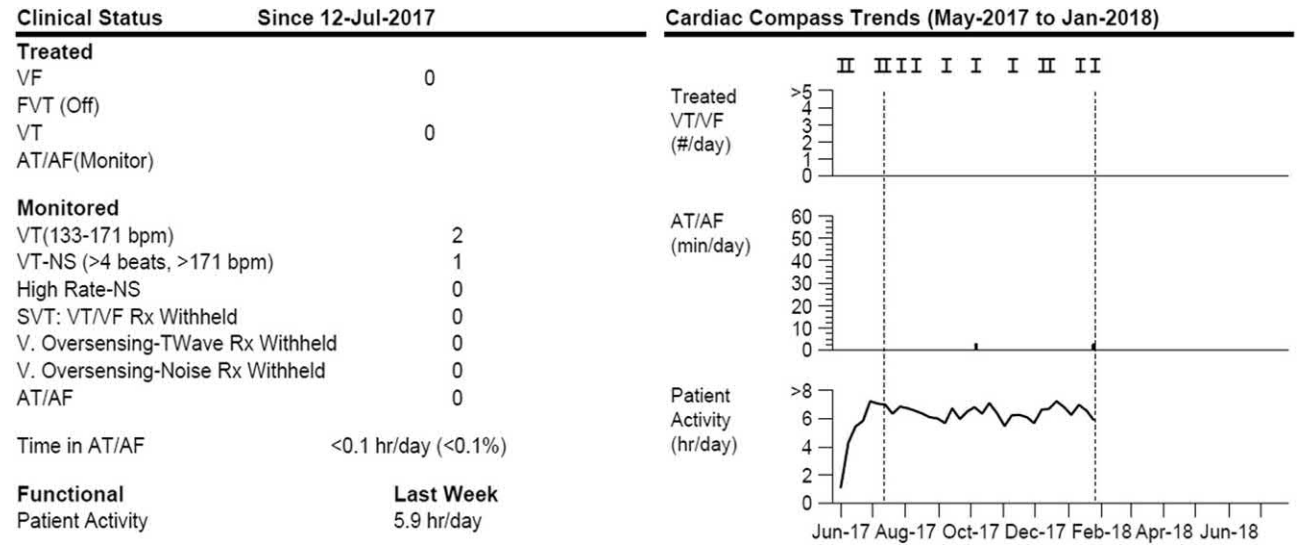

FIGURE 62.7 Monitoring of an ICD in a 24-year-old pregnant woman with hypertrophic cardiomyopathy detected two episodes of nonsustained ventricular tachycardia. Pregnancy and caesarean delivery were uncomplicated. *ICD*, implantable cardioverter defibrillator.

pregnancy [5]. Single-chamber devices should also be preferred. If indication emerges during pregnancy, ICD implantation is recommended using echocardiographic guidance or mapping, especially if the fetus is beyond 8 weeks of gestation (Fig. 62.8) [5]. However, the literature on transesophageal echocardiography use in ICD implantation is limited [41]. Subcutaneous ICD may be considered, as pacing therapy for bradycardia support is not usually needed [30]. However, consideration should be given to the relatively high rate (50%) of spontaneous recovery of peripartum cardiomyopathy after delivery when decisions are made [30]. Uninterrupted wearable cardioverter defibrillator use for up to 6 months can protect these young mothers from dying suddenly and yields important information about a potential permanent risk that will indicate ICD implantation [42,43]. Moreover, the

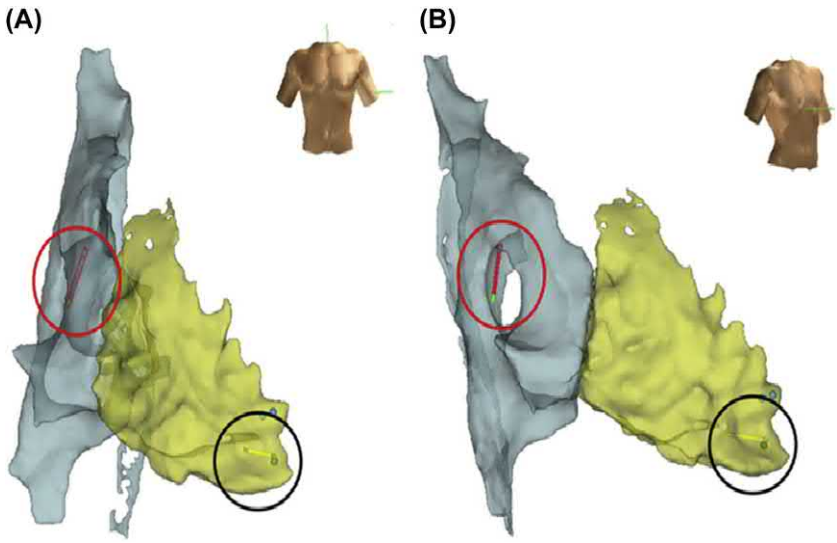

FIGURE 62.8 ICD implantation for secondary prevention of sudden death in a 38-year-old woman with mitral valve prolapse and a sudden cardiac arrest in her 24th week of pregnancy. A single-lead ICD with floating atrial sensing dipole was implanted using three-dimensional reconstruction of the right heart structures without using fluoroscopy. The proper positioning of the lead was possible thanks to the simultaneous display of both the atrial and ventricular dipoles on the electroanatomical mapping system. Blue structure represents right atrial, inferior vena cava, and superior vena cava. Yellow structure represents right ventricle. The implantable cardioverter defibrillator ventricular lead tip can be seen in the *black circle*, near the apex of the right ventricle. The floating atrial dipole of the lead is visible in the *red circle*, in the right high region of the atrium ((A) AP projection, (B) RAO projection). *From Quartieri F, Giacopelli D, Iori M et al. Implantation of single lead cardioverter defibrillator with floating atrial sensing dipole in a pregnant patient without using fluoroscopy. Indian Pacing Electrophysiol J. 2016;16(2):70–72 with permission.*

wearable cardioverter defibrillator may also help to avoid unnecessary ICD implantation by providing time for recovery of left ventricular function.

Catheter ablation

Catheter ablation is recommended in patients with recurrent ICD shocks due to sustained VT [30]. The recurrence rate of VT during pregnancy was as high as 27% in a study that examined pregnant women with a history of VT [2]. Performance of catheter ablation as an urgent procedure is justified only in drug refractory cases of incessant VT or electrical storm [30].

Most of these interventions are usually performed with fluoroscopic guidance with the assistance of electromagnetic three-dimensional mapping systems. However, exposure of the fetus to ionizing radiation is a concern during pregnancy. Exposure to a dose of 50 mGy has not been associated with fetal anomalies or pregnancy loss, and this threshold is considered as reasonable, especially between the first and eighth week of pregnancy [7]. The effective dose for patients undergoing catheter ablation of more complex arrhythmias, as ventricular arrhythmias, is typically higher. The median effective dose for a VT radiofrequency catheter ablation is 16.6 mSv and can exceed 45 mSv [44]. The majority of the total radiation dose to the fetus is due to the insertion and advancement of the electrode catheters from the groin to the heart under fluoroscopic guidance. Therefore, insertion of the catheters by the subclavian route instead of the femoral could eliminate direct fetus irradiation [45]. Other strategies to reduce ionizing radiation exposure with conventional radiographic imaging systems include optimization of variables to regulate the amount of radiation and image quality along with the use of radioprotection cabins or suspended operator protection systems [44].

A completely nonfluoroscopic catheter ablation of ventricular arrhythmias has also been demonstrated to be safe and efficient without increase in procedural times as compared with the conventional approach (Fig. 62.9). The insertion and advancement of the catheters has been shown to be feasible with the use of the three-dimensional mapping systems [46]. The use of intracardiac echocardiography can

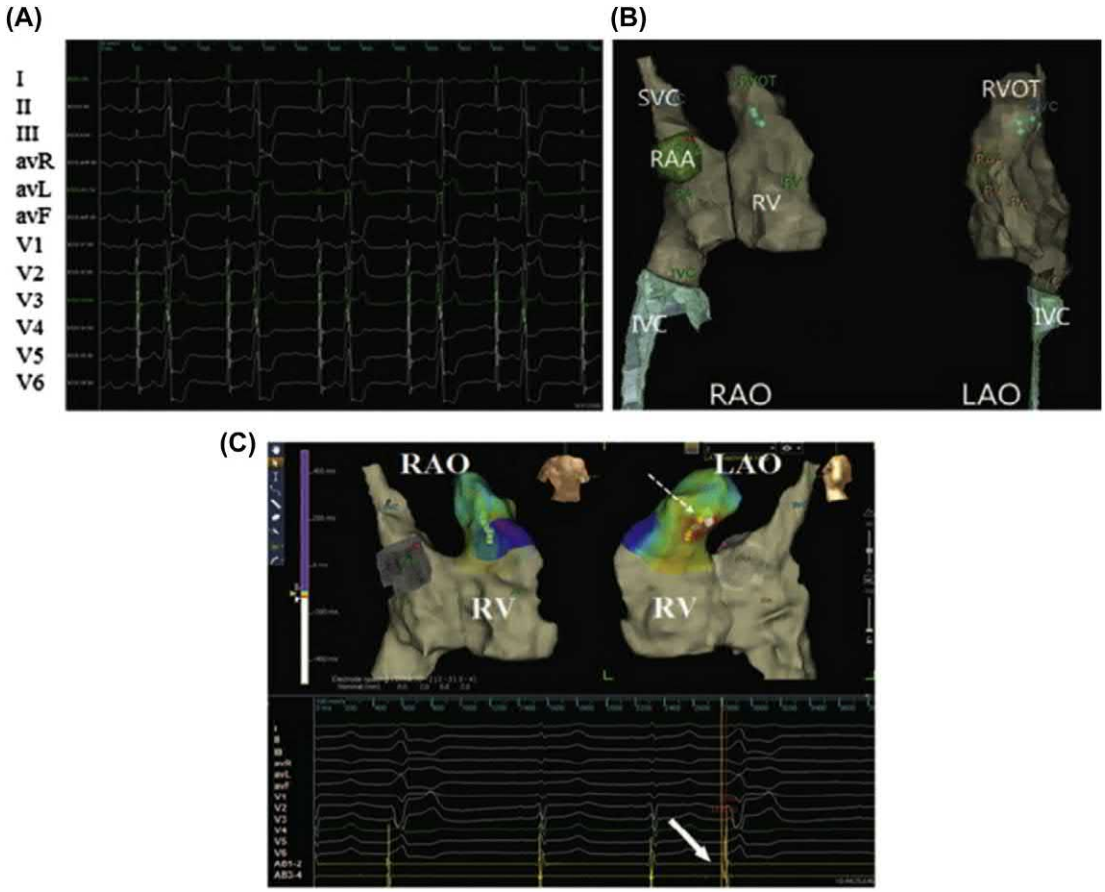

FIGURE 62.9 Catheter ablation for premature ventricular contractions and ventricular tachycardia associated with severe symptoms and refractory to β-blockers in a 33-year-old pregnant at the 31st week of pregnancy. (A) Surface electrocardiogram shows frequent premature ventricular complexes before radiofrequency catheter ablation. (B) Path and geometry-relevant structure during catheter insertion. (C) Electrophysiology study was performed without X-ray exposure guided by the Ensite NavX system. *From Chen G, Sun G, Xu R et al. Zero-fluoroscopy catheter ablation of severe drug-resistant arrhythmia guided by Ensite NavX system during pregnancy: Two case reports and literature review. Medicine (Baltimore). 2016;95(32):e4487 with permission.*

also be useful in more complex procedures, as the catheter ablation of structural VT [47].

Specific populations

In patients with congenital long QT syndrome or catecholaminergic polymorphic VT, β-blockers, preferably nonselective, should be continued during pregnancy and at least 40 weeks after delivery [5,43].

The risk of sustained ventricular arrhythmia seems poorly predictable in pregnant women with arrhythmogenic right ventricular cardiomyopathy and supports the continuation of β-blockers during pregnancy [21].

Although Brugada syndrome is not associated with increased risk of ventricular arrhythmias during pregnancy, consideration should be given to the forbidden analgesic and anesthetic agents used during labor [48].

Conclusion

Although usually benign, ventricular arrhythmias during pregnancy may occasionally be life-threatening. Treatment of ventricular arrhythmias in pregnancy is generally similar as in nonpregnant patients. However, special consideration should be given to potential teratogenic and hemodynamic adverse effects on the fetus. Thus, multidisciplinary cooperation is indicated for optimal treatment. The use of antiarrhythmic drugs must be well justified and provided only when the arrhythmias are associated with severe symptoms, especially hemodynamic compromise. Electrical cardioversion is also safe in all trimesters of pregnancy. Identification of patients in higher risk, as those with structural heart disease, also determines therapeutic approach. More advanced therapies, as catheter ablation and ICD implantation, should ideally be performed before conception when indicated.

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Chapter 63

Pregnancy in Congenital Long QT and Brugada syndrome patients

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The true prevalence of the individual inherited channelopathies is likely underestimated, given the variable penetrance of each of the disease states [1–3], and the lack of symptoms in many carriers of pathogenic gene variants. The inherited arrhythmia syndromes as a whole are rare, with prevalence ranging from 1 to 2000 for both long QT syndrome (LQTS) and Brugada syndrome (BrS) [4,5]. There is conflicting evidence for the role of cardiac genetic variants and primary arrhythmia syndromes in the pathogenesis of sudden infant death syndrome (SIDS) [6–8]. There is evidence, however, that a proportion of cases of SIDS (~4%) are due to genetic heart disease [9–11]. This reinforces the importance of recognizing affected parents and extending screening to identify newborns who may also benefit from basic cardiac screening. Clinical genetic testing is available for most inherited arrhythmia disorders, and if a pathogenic gene variant is identified, cord blood testing at the time of delivery may be considered. As the depth of understanding of genetic variation grows, the classification of gene variants may change over time [12]. The interpretation of any identified genetic variants should be guided by experienced clinicians, as should any subsequent recommendations for further family screening [13,14].

The approach to managing primary arrhythmia syndromes during pregnancy includes clinical screening to identify potentially high-risk features, avoidance of arrhythmia provocation, arrhythmia prophylaxis when possible, and appropriate neonatal screening. The labor and delivery plan should include consideration of individual maternal risk factors and history of symptoms or arrhythmia. In general, unassisted vaginal delivery is recommended for women with a primary arrhythmia condition and no significant structural cardiovascular disease or obstetric contraindications [15]. Women with LQTS or BrS may be at increased risk of arrhythmia upon exposure to certain drugs, and an awareness of these agents is critical to anesthetic planning [16,17]. Increased adrenergic tone secondary to either emotional or physical stress can trigger potentially life-threatening arrhythmias in women with LQTS [18]. During the active phase of labor, most women will demonstrate heart rate elevation that can approximate their maximum estimated heart rate [19]. Strong consideration may be given to the use of epidural anesthesia and assisted delivery or caesarean section for women who are considered to be at elevated risk of arrhythmia. Although this is a common approach, the impact of the mode of delivery and anesthetic management on sympathetic tone and circulating catecholamine levels in both mother and fetus is not well studied. In actuality, there is significant variability among the small studies that have been published [20–23]. Rhythm monitoring should be considered during labor and delivery for women with a prior history of cardiac arrest or hemodynamically significant ventricular arrhythmia.

Long QT syndrome

LQTS is a condition characterized by abnormal myocardial repolarization that is manifest as QT prolongation on the surface ECG [24]. A specific form of polymorphic ventricular tachycardia, Torsades des pointes (TdP), is the arrhythmia classically associated with LQTS. It is a triggered arrhythmia that can result in syncope or sudden death in this condition [25]. Examination of the electrocardiogram is the basic screening test for LQTS. The upper limit of normal for the corrected QT interval in women is 460 ms, but an affected individual or gene carrier may have a normal QTc on screening ECG [26,27]. The diagnosis of LQTS is made based on characteristics of the ECG alone, or a scoring system that incorporates clinical and historical factors [28,29]. There are many genetically distinct LQTS subtypes [30], but the majority of cases are result from

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genetic variations that cause loss-of-function mutations in potassium channels. In LQT1, the gene that encodes the slowly activating delayed-rectifier potassium channels, KCNQ1, is responsible for the clinical phenotype. In LQT1, events are typically seen at elevated heart rates, as the result of physical or emotional stress. Diving and swimming in particular have been identified as potent arrhythmia triggers in LQT1 [31]. In this subtype, the QT may be prolonged at rest, or abnormal repolarization can be provoked with exercise challenge, particularly at maximum heart rate [32,33]. In LQT2, a loss-of-function mutation in KCNH2, the gene that encodes the rapidly activating delayed-rectifier potassium channels, is responsible for QTc prolongation. In this subtype, arrhythmia triggers more frequently include sudden arousal, such as strong acoustic stimulation [34]. The QT can be prolonged at baseline, or provoked by sudden changes in heart rate from a resting state, or during recovery from exercise [33]. Despite the finding of characteristic ECG appearances and arrhythmia triggers in these common subtypes, these patterns are not exclusive, and events in any subtype may occur at rest, or with a wide variety of physical activities [35].

Pregnancy has an important impact on arrhythmia outcomes in women with LQTS [36,37]. There is some variability in the literature regarding risk of arrhythmia during gestation, but most data indicate that the period of greatest vulnerability to arrhythmia spans the first 9 months postpartum [37–39]. In the earliest description of pregnancy outcomes in women with LQTS, the incidence of arrhythmia events (syncope and sudden death) in 111 women with LQTS was 3.8% prior to becoming pregnant and 9.0% during pregnancy. The rate of events substantially increased to 23.4% in the first 9 months after delivery [36]. The observed increase in risk of postpartum events remained elevated, even when low-risk women, with no events prior to pregnancy, were considered. In this group, 9.0% had cardiac arrest or syncope postpartum. In this early study, few women were treated with a beta-blocker over the course of observation. Subsequent studies of women with LQTS in pregnancy showed that the genetic subtype of LQTS was also associated with differences in pregnancy-related arrhythmia risk [38]. It is clear that adverse cardiac outcomes increase in after delivery in both LQT1 and LQT2, but most occur in women with LQT2 [37,38]. Postpartum events, including syncope, life-threatening arrhythmia, or death, are <1% in LQT1 compared to 16% in LQT2 [38]. Fortunately, intrapartum arrhythmia events have not been reported in LQTS [19,37]. The factors that account for the increase in cardiac events after delivery in LQTS are not well understood. Declining levels of estrogen have been shown to increase the expression of adrenergic receptors in the myocardium [40] and may also influence alter intracellular calcium balance [41–43], predisposing to myocardial afterdepolarizations and subsequent arrhythmogenesis. In addition, oxytocin and prolactin may prolong the QT interval by reducing IKs, and promoting afterdepolarizations and subsequent Torsades [44] (Fig. 63.1). Environmental factors have been suggested as important arrhythmia triggers as well. For example, the sudden acoustic stimulation of an infant crying may preferentially trigger a rapid rise in heart rate and arrhythmia in women with LQT2, who are vulnerable to failure of QT shortening in response to abrupt increases in heart rate [45]. Beta-blocker therapy is extremely effective in the prevention of adverse cardiac events in LQTS and is considered first line for arrhythmia prophylaxis in this condition [46]. It is recognized that beta-blockade has the greatest efficacy in patients with either LQT1 and LQT2 [18,47]. There is strong evidence supporting the efficacy of beta-blockade as well in the prevention of arrhythmia events in pregnancy [37,48]. Beta-blockade reduces cardiac event rates after delivery, with only 0.8% of women who were taking a beta-blocker postpartum experiencing syncope or cardiac arrest, compared to 3.7% of women not taking beta-blocker [37]. The selection of beta-blocker for use in pregnancy must consider the safety profile for use in pregnancy as well as compatibility with breastfeeding. The beta-blockers with demonstrated efficacy in LQTS include nadolol, propranolol, metoprolol, and atenolol [49–51]. There is an

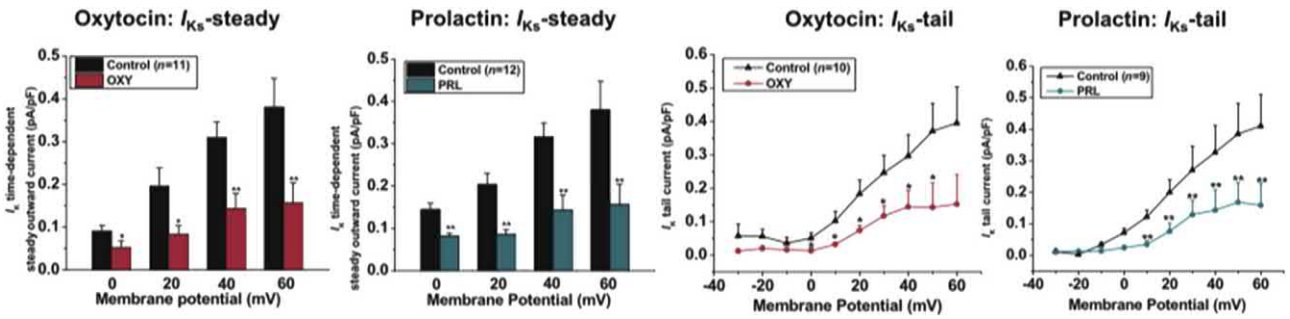

FIGURE 63.1 Hormone effects on IKs currents in LQT2 rabbit cardiomyocytes showing significant IKs steady current amplitude and IKs tail current attenuation after oxytocin and prolactin exposure, when compared to baseline controls.(Europace (2019) 0, 1–13) (original figure 4) *With permission from the European Society of Cardiology.*

abundance of data to support the safety of metoprolol, propranolol, and nadolol (all pregnancy risk Category C) for use in pregnant women [1,52], whereas atenolol (pregnancy risk Category D) should not be used, as it is associated with significant intrauterine growth restriction [53]. These drugs appear to have equal efficacy overall, but nadolol is most effective in LQT2 patients who are deemed higher risk, including those with QTc >500 ms, or with a history of cardiac arrest or syncope [47]. There is some evidence that the shorter acting formulation of metoprolol, with twice a day dosing, is less effective than propranolol or nadolol particularly in individuals with a prior history of syncope or cardiac arrest [54].

Nadolol is the beta-blocker of choice in LQT2, particularly with QTc >500 ms, and in high-risk individuals with LQTS [49–51,54]. The typical nadolol dose used in LQTS is 1—1.5 mg/kg/day. Data regarding the use of nadolol in pregnancy remain limited, and for this reason, its use should be limited to women at elevated arrhythmia risk. The low-protein binding property of nadolol results in a greater degree of secretion into the breast milk than propranolol or metoprolol [55,56]. Secretion into breast milk, combined with its long serum half-life and dependence on renal clearance, renders it likely to achieve detectable levels in the neonate, although this has not been directly evaluated. It is predicted that a breastfeeding infant would receive about 5.1% of the total maternal dose. The American Academy of Paediatrics has determined that nadolol is compatible with breastfeeding [57]. However, when nadolol is used postpartum, nursing infants should be monitored for symptoms of beta blockade. Propranolol, a noncardioselective beta-blocker may be considered if an alternative beta-blocker is needed. Propranolol has a low risk for accumulation in the breastfeeding infant [57]. Bisoprolol is being used with increasing frequency in the management of LQTS, particularly LQT1 [58,59]. To date, however, the small sample sizes and paucity of data regarding its use in pregnancy precludes routine use for arrhythmia prophylaxis in pregnancy.

Guidelines for management of LQTS during pregnancy have not yet been established. Important guiding principles include the identification of women at risk, confirmation of the diagnosis for appropriate management when indicated, and screening for high-risk features which include a history of cardiac arrest, syncope, or a QTc >500 ms. Beta-blocker therapy is indicated for the purpose of arrhythmia prophylaxis. Beta-blocker therapy is titrated to blunt peak exertional heart rate, and to ensure that the resting heart rate remains <100/min. Ambulatory ECG/Holter monitoring may have practical utility in observing heart rate trends over 24 h. Maximal treadmill stress testing is not routinely performed during pregnancy to guide beta-blocker titration, but it may be considered in high-risk women. Women with suspected LQTS on the basis of family history or abnormal baseline ECG may undergo supervised exercise stress testing to evaluate QT dynamics, in order to confirm a diagnosis of LQTS to optimize management during pregnancy, and to plan for postpartum care.

A multidisciplinary approach is essential to planning labor and delivery. Women with no prior syncope or cardiac arrest who are stable on beta-blocker therapy can be managed conservatively and proceed with spontaneous vaginal delivery, unless obstetric or fetal factors dictate otherwise. The influence of analgesia on sympathetic tone is not well studied. Decisions regarding anesthetic management should be made according to perceived obstetric risk and maternal preference [23]. Maternal cardiac rhythm monitoring during labor is not indicated. Intrapartum arrhythmia events are very uncommon [60].

Any exposure of an individual with LQTS to pharmacologic therapy should be carefully reviewed for the likelihood of QT prolongation [17]. Oxytocin, an agent that is frequently used during labor and delivery, can potentially prolong the QT interval, but should not be avoided if clinical circumstances mandate its use [61,62]. A reasonable approach to therapy with oxytocin in a woman with LQTS includes optimization of serum potassium and magnesium levels, and evaluation of the 12-lead ECG prior to drug administration, and 1–2 h after oxytocin is initiated. Oxytocin should not be continued if the QTc exceeds 500 ms or increases by 60 ms when compared to baseline [63,64]. Although active pushing during labor would be expected to increase the heart rate to near a woman's maximal heart rate, adequate beta-blocker therapy would be expected to blunt this response. Active pushing should not be discouraged in a female who is otherwise low risk [65].

The rare but dreaded arrhythmia complication of LQTS is TdP, which may lead to syncope or cardiac arrest. This arrhythmia requires immediate recognition and initiation of therapy. Defibrillation is indicated for sustained ventricular arrhythmia. Active pharmacotherapy must be reviewed, and any use of QT prolonging drugs should be discontinued. Correction of any electrolyte imbalance, particularly hypokalemia or hypomagnesemia, should be immediately initiated. Bradycardia or pauses in the heart rhythm can be managed with temporary cardiac pacing. Lidocaine or isoproterenol can be useful for the management of on-going arrhythmia [1,66,67].

Planning for neonatal screening is an essential part of managing a pregnancy in the setting of an LQTS parent, particularly in light of the potential role of LQTS in some cases of sudden infant death [68–70]. The risk of cardiac events in a neonate with LQTS may be as high as 4% in the first year of life [68]. Fetal bradycardia may be the first evidence of underlying LQTS [71,72]. Newborn screening can include cord blood testing if a pathogenic variant has been identified in one of the parents. In cases where genetic testing is not available, or if a pathogenic variant has not

been identified in the course of parental screening, genetic testing cannot be offered for the purpose of LQTS screening. In these cases, longitudinal clinical evaluation of the child in consultation with a pediatric cardiologist is recommended [14,70].

Brugada Syndrome

BrS is an inherited condition of impaired myocardial repolarization. Variations in the gene encoding the cardiac sodium channel (SCN5A) are associated with the BrS phenotype [73], but in many cases a causative gene mutation cannot be identified [74]. The ECG signature of BrS consists of >2 mm J-point elevation in addition to >2 mm coved ST segment elevation in at least one of leads V1−V3 [75]. These ECG changes may be transient and not apparent on all ECGs from the same individual. Individuals with BrS may be vulnerable to ventricular arrhythmias, with the risk of syncope or cardiac arrest [76]. Arrhythmia events are typically reported during sleep, or in association with fever. An additional risk for potentially lethal arrhythmias is exposure to drugs that interfere with the ion channel involved in the first phase of myocardial depolarization. The rate of arrhythmia events in women with BrS does not appear to be modulated by pregnancy, or the postpartum state [77,78]. However, women who have high-risk features should be considered for ICD implantation [79]. Clinical features which indicated a higher risk of arrhythmia in BrS include a history of syncope of likely arrhythmic origin, or a history of cardiac arrest [79,80]. The management of a pregnant woman with BrS is generally conservative, with counseling regarding management of fever and avoiding the use of medications that may promote arrhythmia. The medications to be avoided in BrS can be found at the website www.brugadadrugs.org [16]. The medications that may lead to arrhythmia vulnerability include sodium channel blocking agents, which are commonly used for management of cardiac arrhythmias, as well as anesthetic agents such as bupivacaine, lidocaine, and propofol. At present, there are no clinical features that identify a fetus with BrS. However, pathogenic variation in the SCN5A gene can lead to a spectrum of cardiac phenotypes including sinus bradycardia [81], ventricular arrhythmias, which can lead to hydrops or intrauterine demise [82], and conduction abnormalities including high-grade AV block [83].

High-risk women who have a history of syncope, ventricular arrhythmia, or cardiac arrest should have cardiac rhythm monitoring during labor and delivery. Women with no high-risk features can be managed conservatively and proceed with spontaneous vaginal delivery, unless obstetric or fetal factors dictate otherwise. Arrhythmia complications during labor and delivery have been reported in the literature, although they are exceedingly rare [84]. Ventricular fibrillation must be managed immediately with defibrillation, and recurrent arrhythmia can be managed acutely with the administration of isoproterenol [85,86]. If required, oral therapy with quinidine (pregnancy risk Category C) can achieve arrhythmia suppression in women with frequent recurrent arrhythmia [84], but ICD implantation is absolutely indicated in this circumstance.

Genetic testing can be offered to an affected parent, in order to facilitate family screening via genetic testing if a pathogenic gene variant is found. If a pathogenic variant is not identified, or genetic testing is not possible, then cord blood testing should not be offered. In this case, clinical screening of the newborn with 12-lead ECG and consultation with a pediatric specialist is recommended [14].

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Chapter 64

Pregnancy and implanted devices

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Introduction

Heart disease remains a leading cause of maternal mortality and morbidity, and its incidence in pregnancy continues to rise [1]. Improved management and survival of women with congenital heart disease has led to increasing numbers of women reaching childbearing age [2]. Advances in fertility treatments and maternal medical care, as well as the growing number of women postponing pregnancy until later in life, have contributed to an increased population of older mothers who may have acquired heart disease. Some of these women may have cardiac implantable electronic devices (CIEDs) in the form of permanent pacemakers (PPMs), implantable cardioverter defibrillators (ICDs), or cardiac resynchronization therapy (CRT) devices for their conditions. This has resulted in a rise in the prevalence of women of reproductive age with a CIED.

Some women may present during pregnancy with untreated arrhythmias that require CIEDs. Providing care for these women is often challenging with different dilemmas during the antepartum, intrapartum, and postpartum periods. Although these women are encountered reasonably often in cardiac antenatal clinics, there is a scarcity of data in the literature to help guide their management. The aim of this chapter is to review the management of women who have or require CIEDs during pregnancy and postpartum.

Physiological effect of pregnancy on heart rate and conduction

Pregnancy is associated with a number of important cardiovascular physiological changes, which are designed to meet the needs of the developing fetus but may prove problematic for women with preexisting heart disease.

To achieve the needed increase in blood flow to the fetus, cardiac output increases by the fifth week of gestation and thereafter steadily to 50% above prepregnancy levels by 16–20 weeks' gestation [3]. This rise typically plateaus after 20 weeks' gestation and remains elevated until term [4]. The increased cardiac output is associated with increases in stroke volume and heart rate. Heart rate increases gradually throughout pregnancy by 10–20 beats per minute (bpm), reaching a maximum increase of 20%–25% above baseline in the third trimester (Fig. 64.1) [5–7]. There is recent evidence to suggest that estrogen may play a role in this increase in heart rate by altering cardiac repolarization by increasing L-type Ca^{2+} current release from the sarcoplasmic reticulum and accelerating cardiac automaticity [8]. The inability to adapt to these physiological changes may uncover an undiagnosed cardiac condition, which is why some call pregnancy "nature's stress test" [9].

Physiological structural changes, in the form of dilatation of the cardiac chambers and increased left ventricular mass, take place to accommodate the increase in preload due to the increased circulating blood volume [6,10]. The chamber stretch can facilitate arrhythmias by altering the depolarization of the membrane potential [11].

Preconception counseling and risk assessment

Most young women have PPMs implanted because of congenital complete heart block, and less often sinus node dysfunction (SND), atrioventricular (AV) block, neurocardiogenic syncope, and iatrogenic AV node ablation for supraventricular tachycardia. Some may have underlying congenital heart disease. Those with ICDs usually have inherited cardiomyopathies. When the device has been implanted early in childhood, several lead and generator changes may have taken place; leads may be endo- or epicardial, and generators may be implanted in a variety of places, including in the abdomen [12].

Management in pregnancy and risk of an event is largely dependent on the underlying cardiac condition.

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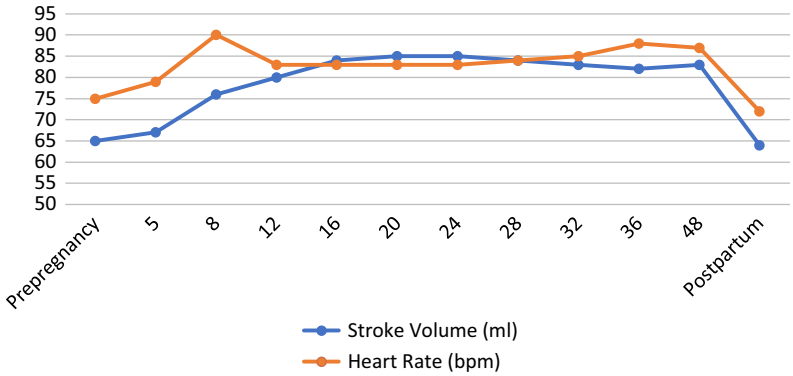

FIGURE 64.1 Increase in stroke volume and heart rate throughout pregnancy. *Adapted from Hunter S, Robson S.C. Adaptation of the maternal heart in pregnancy. Br Heart J 1992;68(6):540–543.*

The risk due to the CIED itself is small. However, several device-related issues need to be borne in mind:

1. Device position

It is important to document the position of the leads and generator and assess how these might be affected by a growing uterus.

2. Adjustment of device

Women who have had PPMs implanted for sinoatrial disease are not able to increase their heart rate appropriately in pregnancy and therefore need their lower tracking rate to be increased by 10–20 bpm for the duration of the pregnancy and adjusted again several week postpartum.

2. Recurrent arrhythmias

These are common in pregnancy, particularly in those who have been previously affected. Women need to be counseled that their arrhythmia may recur [13]. Thorough evaluation allows for the opportunity to adjust pharmacologic agents appropriate for pregnancy, optimize the woman's condition, and deal with other comorbidities that may have an adverse effect on pregnancy as well as optimize any CIED.

3. Inheritance

The increased risks of fetal cardiac anomalies in mothers' with congenital heart disease and the likelihood of the baby of also having an inherited cardiac condition from their mothers' should be discussed. Genetic testing can be done in pregnancy, if it has not been done prior to conception. Where a neonate may manifest the condition in the neonatal period, there must be review by a pediatrician prior to discharge home.

Maternal risk of cardiac complications in preexisting heart disease can be estimated using a number of risk scores and calculators, based on the disease-specific risk, such as the modified World Health Organization (mWHO) classification [14], CARPREG (CARdiac disease in PREGnancy), ZAHARA, and ROPAC (Registry Of Pregnancy And Cardiac disease) [1,14–16].

Preconception counseling and assessment also provides an opportunity for CIED implantation prior to pregnancy in women with known hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy, or arrhythmogenic conditions who have a high risk of sudden cardiac death and those who have suffered a previous cardiac arrest, if not already done [17].

Implantable cardioverter defibrillators during pregnancy

No specific guidelines exist on the management of ICDs during pregnancy, as the data published are limited and based on four retrospective studies (one multicenter and three single-center) and case reports.

Natale et al. published the first and largest (multicenter retrospective) study of 44 pregnant women with ICDs [18]. Their underlying cardiac conditions were long-QT syndrome (13 patients), idiopathic ventricular fibrillation [17], cardiomyopathy [8], congenital heart disease [3], coronary artery disease with an ischemic cardiomyopathy [1], idiopathic hypertrophic subaortic stenosis [1], and right ventricular dysplasia [1]. 42% of these women (95%) had abdominally implanted generators for secondary prevention. 25% (11 of 44 patients) experienced a device shock. No adverse fetal outcomes were evident as a result of the shocks. It is noteworthy that there was no increase in the number of shocks in these women during pregnancy compared with prepregnancy. In those that had vaginal deliveries, strong uterine contractions did not precipitate any arrhythmias or ICD discharges. Eight (18%) had a medical or device-related complication. The device-related problems included tenderness at the pocket scar [2], generator migration [1], and pericarditis secondary to the epicardial patches [1]. Medical complications included pulmonary embolism [1], therapeutic abortion not related to device [1], worsening hyperthyroidism [1], congestive heart failure [1], and weight loss [1].

Miyoshi et al. demonstrated no increased incidence of an ICD-related complication in six women [19]. Even though the number of episodes of nonsustained VT increased toward the end of the second trimester, no ICD

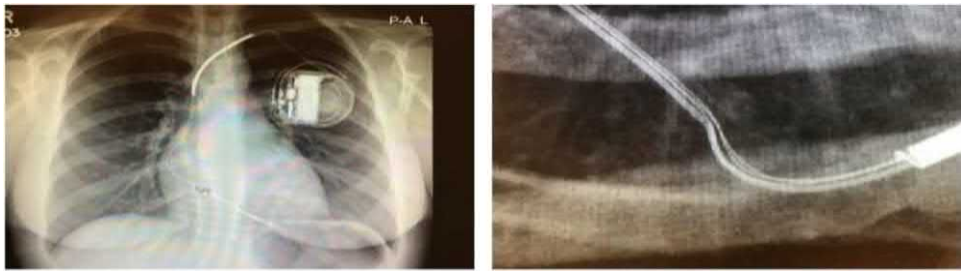

FIGURE 64.2 The panel on the left shows a posteroanterior chest X-ray of a woman who was 8 weeks' pregnant with an area of indentation of the ICD lead suggestive of probable "rib crush." The panel on the right shows a magnified image of the indented lead. *ICD*, implantable cardioverter defibrillator.

discharges occurred during pregnancy, and only one woman received antitachycardia pacing at 27 weeks' gestation. β-Blockers were uptitrated for these arrhythmias. All deliveries were by cesarean section for obstetric reasons. The ICD was turned off for five of the six patients, and electrocautery was not used. Three of the fetuses (50%) had fetal growth restriction (on two cases, the mother had received β-blockers).

Schuler et al. reported the results of a single-center retrospective study of 14 women in the United Kingdom. Their results showed a lower ICD shock rate when compared with Natale et al. (5.3% vs. 25%), but only 36% (5 of 14) women versus 95% had the device implanted for secondary prevention [20]. Arrhythmias (4, 21.1%) and heart failure (2, 9.1%) were also reported. ICD-related complications were in the form of atrial lead fracture found on follow-up (1/5 switching to VVI mode, 5.3%) and lead-related thrombus in a factor V Leiden patient (1, 5.3%). There were no inappropriate device shocks or therapies. Deliveries were uneventful with the recorded mode of delivery for the majority being vaginal. ICDs were programmed into "monitor only" mode during elective caesarean section to avoid electrical interference from diathermy and immediately reprogrammed to full therapy mode postoperatively.

A French group looked at the outcomes of 20 pregnancies in 12 women, all of whom had prepectoral ICD devices with bipolar endocardial leads [21]. Nine of these women had their ICD implanted for secondary prevention, one of whom presented with an out-of-hospital cardiac arrest, having had 12 shocks for ventricular arrhythmias and incidentally found to be 6 weeks' pregnant. One woman, after receiving two shocks from her ICD during an episode of ventricular fibrillation, miscarried at 4 weeks' gestation. It was observed that an adverse outcome might arise from an ICD shock in the very early stages of pregnancy. No device-related complications, such as lead dislodgement, lead dysfunction, or lead thrombi, were reported.

ICD-related complications are uncommon in pregnancy, but when they do occur, they should be managed in a center with expertise in both cardiac obstetrics and lead extraction. Fig. 64.2 shows the chest X-ray of an 8-week pregnant woman with myotonic dystrophy and LQT2. She experienced an inappropriate shock, and device interrogation demonstrated a rise in lead impedance suggestive of a lead fracture. This can be seen as an indentation on the X-ray. The lead was extracted using a cutting sheathe technique with an internal extraction wire and gentle traction. On removal of the existing lead, two different areas of break were seen suggestive of subclavian/rib crush. A new lead was deployed in the right ventricular apex and attached to the generator with excellent thresholds and sensing. Cardiac surgical backup was available, and minimal fluoroscopy was used (total X-ray screening time of 1.24 min and screening dose of 0.03 Gy cm^2) with lead shielding of the abdomen to protect the fetus.

β-Blockers are often given in women with ICDs to suppress arrhythmias and avoid both appropriate and inappropriate ICD shocks [22]. Their usage during pregnancy is associated with intrauterine growth retardation, low birth weight, and neonatal hypoglycemia [23]. Nonetheless, β-blockers significantly lower the risks of mothers with structural heart disease or congenital heart disease from developing episodes of life-threatening ventricular arrhythmias and outweigh the potential risk to the fetus [14]. With regular fetal growth scans performed during pregnancy as well as close monitoring of neonatal glucose levels postpartum, good outcomes can be achieved for the baby 6 months postdelivery [21].

Permanent pacemakers during pregnancy

Women with PPMs and a structurally normal heart are of low risk. A dual-chamber permanent pacemaker does not interfere with the normal course of pregnancy; it allows the heart to adapt to the increased workload required during pregnancy, with the proviso that atrial rate will not increase spontaneously in sinoatrial disease (see earlier). In women with a fixed-rate pacemaker, the required increase in cardiac output can be achieved with a compensatory increase in stroke volume. The different pacemaker modes can be found in Table 64.1.

TABLE 64.1 Revised NASPE/BPEG generic code for pacing.

I	II	III	IV
Chamber paced	Chamber sensed	Response to sensing	Rate adaptive
O = none	O = none	O = none	O = none
A = atrium	A = atrium	I = inhibited	R = rate adaptive
V = ventricle	V = ventricle	T = Triggered	

At the time of preconception counseling or early in the first trimester, women with a pacemaker should receive a clinical assessment, an electrocardiogram, transthoracic echocardiogram, and device interrogation. Symptoms of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and reduced exercise intolerance should be sought throughout pregnancy. Although some of these are commonly reported symptoms in normal pregnancy, further evaluation may be needed at times to assess the significance of the symptoms as well as pacemaker interrogation and adjustments.

Our group previously reported on 11 women (16 pregnancies) with permanent pacemakers (eight prepectoral, one subpectoral, and two abdominal devices) for known atrioventricular block [24]. There were no complications related to the generators or leads during any of these pregnancies. Three women had maternal complications, all relating to their underlying structural condition. One woman was induced at 38 weeks after developing cardiac decompensation in the third trimester. A second with a previous atrial septal defect repair had brief runs of atrial fibrillation. Both had uneventful deliveries and postpartum courses. A third woman with known Ebstein's anomaly had previously undergone tricuspid valve repair followed by mechanical valve replacement prior to pregnancy. She developed progressive right ventricular impairment and had an intrauterine fetal death at 20 weeks gestation, due to warfarin.

Hidaka et al. studied 10 deliveries from their center as well as 10 case reports (12 deliveries) in women who had PPM implantation prior to delivery [25]. Only one of 21 pregnancies developed significant pulmonary edema, while all other deliveries had good ante- and postnatal outcomes. The most common complications they reported were skin irritation/ulceration at the site of implantation, battery failure, and extrasystoles.

Pacemaker malfunction is rare during pregnancy with only a few cases published. A rare case of complete transection of an epicardial pacing lead due to significant stretch during the last trimester of pregnancy as a result of crossing the abdominal wall from the right to the left side has been reported [26]. Planning of the epicardial lead positioning and site of the device pocket should be carefully considered in female patients, keeping in mind that they may wish to conceive in the future.

Another report of malfunction in the form of nonreversible increased right ventricular (RV) lead pacing threshold that led to early generator depletion was described in a 22-year-old lady who presented with syncope in her second trimester [27]. At 30 weeks of pregnancy, the generator was replaced with a dual-chamber device, but a high RV lead pacing threshold persisted, even 6 months postnatally. The authors felt that this may be due to microdislodgement of the RV lead as a result of a lack of enough slack of the lead before pregnancy. They also proposed the possibility of the effect of hormonal changes during pregnancy and that permanent myocardial tissue changes might have some role in changing the pacing threshold.

Implantation of implantable cardioverter defibrillator during pregnancy

The need for an ICD is usually identified before pregnancy. However, if an ICD is required during pregnancy, the indication must be clear, and all other alternatives must be explored. However, if needed, it can be performed safely, especially beyond 8 weeks' gestation [14]. Radiation exposure to the fetus should be as low as reasonably achievable (ALARA) [28]. This can be minimized by the use of lead shielding of the abdomen, collimation of the X-ray beam specifically to the area of interest, and minimal use of fluoroscopy. The risk of fetal anomalies or pregnancy loss is negligible when radiation exposure doses are $\leq$50 mGy [29]. Successful implantation can be performed safely in selected pregnant patients by echocardiography and electroanatomic mapping system guidance without the use of fluoroscopy [30,31].

Need for permanent pacemaker implantation in pregnancy

SND is rare in pregnancy, even more so in women with structurally normal hearts. It may be seen in women with cardiomyopathies or in those who have undergone surgical repair of CHD involving the right atrium, for example, in Mustard, Senning, or Fontan repairs. Rarely, sinus bradyarrhythmia may occur as a result of compression on the inferior vena cava by the growing fetus [14].

Li et al. described 104 episodes out of 100,000 pregnancy-related admissions that were due to sinus

tachycardia, sinus bradycardia, or sinus arrhythmia [32]. The exact number of these episodes was likely an underestimate, as these arrhythmias are not necessarily associated with symptoms. A case of persistent bradycardia (~40 bpm) in a 32-year-old woman throughout the entire course of labor has been reported. She experienced dizziness during labor. Despite her initial reluctance, epidural anesthetic was administered, and subsequent labor was uneventful. The bradycardia spontaneously resolved immediately postpartum delivery. Prior to the onset of labor, she had a baseline heart rate of 90–100 bpm and no known structural heart disease.

Advanced atrioventricular conduction block (AVB), in the absence of structural heart disease, is also rare during pregnancy. If AVB develops during pregnancy, it is usually well tolerated, and the majority of cases can be closely monitored without the need for PPM implantation during pregnancy or delivery [24]. The need for urgent PPM during pregnancy is uncommon with few reports in the literature. It may be diagnosed as an incidental finding on an electrocardiogram performed for other reasons, or it may manifest with symptoms such as dyspnea, presyncope, and syncope. In symptomatic patients, temporary pacemaker implantation or even permanent pacemaker implantation may be necessary before labor. Table 64.2 summarizes the clinical course and use of pacing from the literature. Recently, a zero fluoroscopy pacemaker implantation can be achieved with three-dimensional electroanatomical mapping [33]. If fluoroscopy is used, the same precautions for radiation exposure to the fetus should be taken as mentioned for ICD implantation.

In our center, three out of four patients who presented for the first time in pregnancy with previously undiagnosed conduction disease required a permanent pacemaker (two patients during and one after) [24]. Device implantation was performed under fluoroscopic guidance and abdominal protection with lead shielding. Three women with known but untreated atrioventricular conduction disorder developed increased severity of atrioventricular conduction block and/or bradyarrhythmia during pregnancy. They were carefully followed up, and the severity resolved postpartum without the need for pacing. This observation suggests that atrioventricular conduction block during pregnancy may resolve postpartum, implying that pregnancy itself may affect the conduction system. We hypothesized that an increase in the mechanical stretch and size of the atria may elicit or increase the conduction disturbance in the pregnancy state [23]. The evidence of increased atrial stretch and size during pregnancy to accommodate the increased volume load is supported by the increase in atrial natriuretic peptide levels found in pregnancy compared with the nonpregnancy state [34–38].

Hidaka et al. reported on 22 of their own and 13 patients in the literature that had complete AVB with no PPM during pregnancy. None of their own patients required a permanent PPM while pregnant. Before 1997, 10 of their patients received prophylactic temporary pacing. Following the implementation of a new protocol at their institution, standby pacing was made available for nine women antenatally, but pacing was not required. This change in protocol took place as the authors stated that the need for pacing, optimal timing, and rate settings were not well defined. The 13 case reports they compiled showed that two women required PPM during pregnancy. Among the remaining 11 cases, four were managed with prophylactic temporary pacing during the intrapartum period.

In a retrospective study of 136,422 pregnancy-related admissions to a single obstetric unit over the course of 9 years, the prevalence of arrhythmia-associated admissions was 166/100,000 with two patients (frequency of 1.5/100,000) presenting with a high degree of atrioventricular block [32]. Only one of these women required a temporary transvenous pacemaker for third-degree heart block and hypotension during labor. She had previously unrecognized congenital complete heart block, which necessitated a PPM after birth. The other woman developed transient Mobitz type II second-degree AVB from a vasovagal reaction during labor. No pacemaker was required.

Delivery with cardiac implantable electronic device

When a woman with a CIED is admitted to the delivery suite, the clinical team should refer to the delivery plan put in place by the joint obstetric, cardiac, and anesthetic team during the patient's antenatal care. The ultimate goal in the management of these patients is to control the conditions that may precipitate arrhythmias, minimize hemodynamic stress, maintain homeostatic balance, and avoid any factors that may interfere with device function.

Vaginal delivery is the preferred mode of delivery in most cases. Continuous ECG monitoring is not routinely advised during labor, as it is uncomfortable and distracting for the woman and not useful in most cases [39]. A 12-lead ECG can be performed if she develops any concerning symptoms or tachycardia. It is recommended that an ICD remains activated for vaginal delivery. Mothers with sinoatrial disease who are pacing dependent may not have an appropriate tachycardia response to hypotension, and carers need to be aware that any bleeding needs to be monitored carefully.

If the mode of delivery is caesarean section, the most serious concern is the potential adverse effect of electromagnetic interference (EMI) on CIEDs integrity and function. Special precautions must be taken if unipolar diathermy is to be used [40,41]. ICDs can be programmed to "monitor only," or a magnet can be applied to avoid electrical interference from diathermy to prevent inappropriate shock delivery or failure to detect arrhythmias. This prevents damage to the device generator and/or myocardial burns. PPMs can be programmed with a magnet to asynchronous mode, e.g., AOO, VOO, or DOO, to avoid oversensing or inappropriate detection of extrinsic signals to prevent device inhibition [42]. If this is

TABLE 64.2 Outcomes of patients with complete heart block and without pacemaker during pregnancy.

Authors (publication year)	No. of patients	Age or mean age at conception	History of syncope	Use of prophylactic TPM	Obstetrical complication	Intrapartum outcome	Live births	Needed PPM during pregnancy	Needed PPM postpregnancy
Eddy and Frankenfeld (1977)	1	21	No	0	None	Uneventful	Yes	No	1-year postpregnancy
Abramovici et al. (1984)	2	38, 29	No	0	None	Uneventful	Yes	No	NA
Gudal et al. (1987)	1	30	1	0	None	Uneventful	NA	PPM at 10 weeks	NA
Lau et al. (1990)	1	33	1	0	None	Uneventful	Yes	PPM at 29 weeks	NA
Dalvi et al. (1992)	3	20,22,24	2	1	None	Three required temporary	Yes	2	NA
Sharma et al. (2000)	1	24	0	1	IUGR and oligohydramnios	Uneventful	1	0	NA
Mehta et al. (2005)	1	30	0	1	None	Uneventful	1	0	PPM was advised but patient could not afford it
Suri et al. (2009)	4	24. 5	1	1	3 IUGR, 3 PTD			Yes, 1 temporary pacing during labor	3
Hidaka et al. (2011)	22	NA	1	10	1 IUGR, 1 PTD	1 TPM after delivery because of transient dizziness	All	0	1
Thaman et al. (2011)	4	26	1	0	0	Uneventful	All	1	1

Dhiman et al. (2012)	1	22	1	0	0	Required PPM	1	1	0
Mandal et al. (2015)	19	NA	6	0	4 IUGR, 3 PTD	3 required PPM, 10 TPM	All	3	5
Keepanasseril et al. (2015)	1	30	0	0	None in reported pregnancy	None	Yes (six previous pregnancies, four live-births, one spontaneous abortion at 3 months, two still births)	No	NA
Baghel et al. (2016)	1	24	1	1	None	Uneventful	1	0	1
Mohapatra et al 2016	1	26	0	0	0	Uneventful	1	0	1
Kivrak et al. (2017)	1	27	0	1	None	Uneventful	1	0	NA
Ząbek et al. (2018)	1	31	0	0	0	Uneventful	1	0	NA
Soni et al. (2019)	1	24	0	0	0	Uneventful	1	0	NA

IUGR, intrauterine growth retardation; *PPM*, permanent pacemaker; *PTD*, preterm delivery; *TPM*, temporary pacemaker.

done, a cardiologist or pacing physiologist must be present. Ideally, however, bipolar diathermy should be used, and the CIED left alone.

If unipolar diathermy is unavoidable, it should be used in brief 1–2 s bursts with 10 s pauses [43]. The pathway from the diathermy to the return electrode should be away from the CIED, and the current field should be at right angles and not parallel to the pacing leads. Diathermy cables should be kept away from the CIED site. If used, defibrillator/pacing pads should be placed in the anteroposterior position and as far as possible from the device generator [40].

Peripartum cardiomyopathy and device therapy

Peripartum cardiomyopathy (PPCM) is an idiopathic form of cardiomyopathy presenting with heart failure secondary to left ventricular (LV) dysfunction toward the end of pregnancy or in the months following delivery, where no other cause of heart failure is identified [44]. Recovery of LV function from PPCM is variable, and although most who recover have done so by 6 months, others can recover over a long period of time [28,45–47]. Although women are at highest risk of ventricular tachyarrhythmias and sudden death in the acute phase of the disease, the risk persists while the LV is impaired, and this may take even longer than 6 months to recover [48,49]. Recovery of LV function relates in part to size and impairment of the LV at the time of diagnosis, but markers to identify patients at risk for arrhythmic death do not exist, further complicating the dilemma of ICD implantation timing in these women.

Wearable cardioverter defibrillator (WCD) therapy has been proposed as an alternative or bridge to ICD and may also reduce the sudden cardiac death risk in PPCM [50]. In a single-center, prospective study, 9 of 12 patients with PPCM were offered a WCD, of which seven agreed to the therapy [51]. During a median follow-up of 81 days, three patients received shocks for ventricular fibrillation accompanied by loss of consciousness. All of these women regained their LV function on follow-up. In another study, 28 (of 108) PPCM patients with WCD showed LV recovery and the WCD was no longer needed, while 21 (20%) had an ICD implanted as LV dysfunction persisted. Cardiac resynchronization therapy should also be considered in patients with persisting LV dysfunction, as per the ESC Heart Failure guidelines [52].

Conclusion

The majority of women with CIEDs embarking on pregnancy are low risk from a device point of view, and their risk largely relates to their underlying condition. The hemodynamic changes in pregnancy do not pose an increased risk of developing device-related complications. PPMs for sinoatrial disease may need to be adjusted, but devices can generally be left alone during pregnancy and delivery. Women should be seen by the joint cardiac obstetric team and plans for antenatal care and delivery made. Location of leads and devices should be documented. Unipolar diathermy should be avoided if caesarean section is required. Fig. 64.3 summarizes how to manage CIEDs in pregnancy. There is no evidence for adverse fetal outcomes for the majority of pregnancies, but in the case of inherited cardiac conditions, counseling is required to discuss potential inheritance in the fetus.

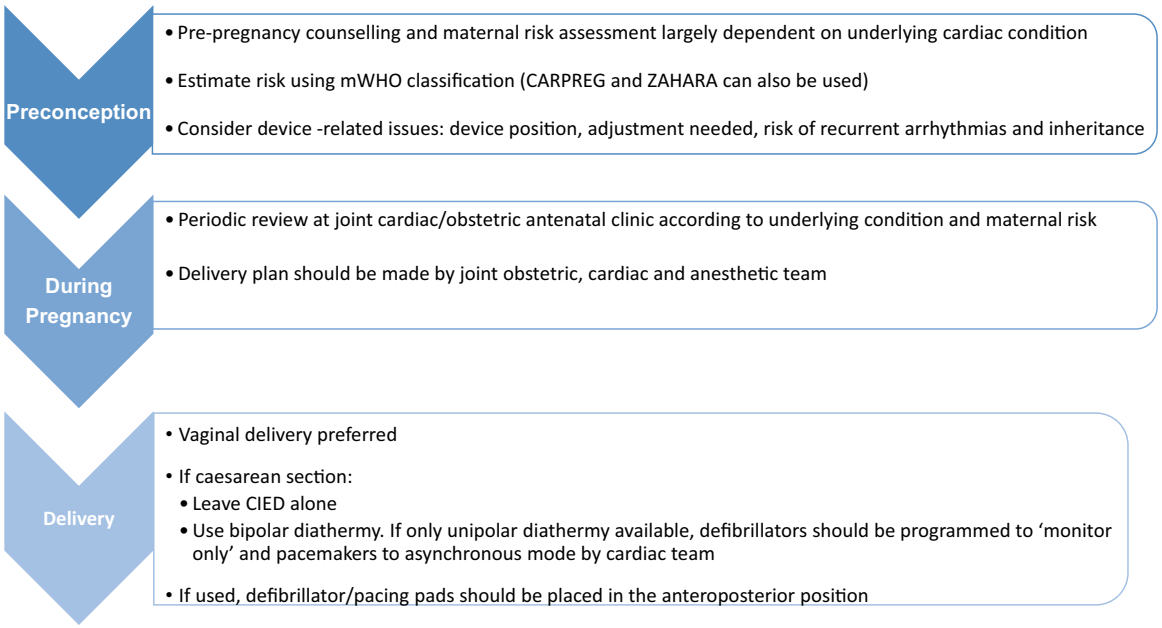

FIGURE 64.3 Management of cardiac implantable electronic devices in pregnancy.

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Chapter 65

Sex and cardiac electrophysiology: fetal arrhythmia in intrahepatic cholestasis of pregnancy

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Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP), also referred to as obstetric cholestasis, is the most common liver disorder that occurs de novo during pregnancy. It is usually diagnosed by elevated maternal total serum bile acid (TSBA) concentrations of $\geq$10−14 μmol/L and maternal pruritus in the absence of a rash, often concurrent with deranged liver enzyme concentrations [1,2]. Ursodeoxycholic acid (UDCA) is the current standard pharmacotherapy for the disease, which has been established to decrease circulating TSBA concentrations in the mother, thereby reversing the dysfunctional fetomaternal bile acid gradient observed in pregnancies complicated by ICP (Fig. 65.1) [3,4]. The elevated TSBA concentrations and pruritus observed in ICP are known to spontaneously resolve during the postpartum period with or without treatment in the majority of cases [5].

ICP is associated with adverse perinatal outcomes including intrapartum fetal distress, neonatal respiratory distress syndrome, and intrauterine death (IUD) [1,2,7,8]. ICP is usually classified as severe when TSBA concentrations reach a threshold of $\geq$40 μmol/L. The risk of perinatal outcomes has been associated with severity of hypercholanemia; specific fetal complications are known to arise when TSBA concentrations rise above thresholds, e.g., spontaneous preterm birth; markers of fetal distress occur when maternal TSBA concentrations are $\geq$40 μmol/L [1,2]. Furthermore, a recent individual patient data meta-analysis demonstrated that the risk of IUD increases in women who have TSBA concentrations of $\geq$100 μmol/L, i.e., an IUD rate of 3.44% compared with the background population rate of 0.32% [9]. TSBA concentrations were found to be the most predictive biomarker for ICP-associated IUD, and other biochemical tests of liver function were not helpful [9].

Bile acids, signaling molecules synthesized and released in response to digestion of food, are formed from catabolized cholesterol. They are conjugated and deconjugated throughout their circulation between the liver and the intestine, resulting in bile acid pool containing primary and secondary bile acids with different amphipathic properties [10]. Therefore, individual bile acids have different cytotoxic properties, and the contents of the bile acid pool can cause different physiological effects [11]. There has been no single mechanism elucidated to explain the role of elevated bile acids in the etiology of ICP-associated IUD, although the current evidence indicates that bile acids induce fetal cardiac dysfunction, which may result in arrhythmia and associated fetal demise.

Although there is a relative paucity of data regarding the role of bile acids in fetal hearts, it is well known that liver disease in adults can lead to cardiac dysfunction [12−14]. Approximately 50% patients with liver cirrhosis develop a multifactorial syndrome known as cirrhotic cardiomyopathy, which can involve QTc interval elongation, contractile dysfunction, cardiac hypertrophy, and dysfunctional cardiac hemodynamics [15].

Cardiac time intervals in intrahepatic cholestasis of pregnancy

Women with ICP have been reported to also have an elongated QT interval length and an increased QT dispersion when using ECG, and these findings were associated with the severity of ICP [16]. However, they were not replicated in fetuses of ICP pregnancies. A recent study showed no difference in QT interval length or ST segment

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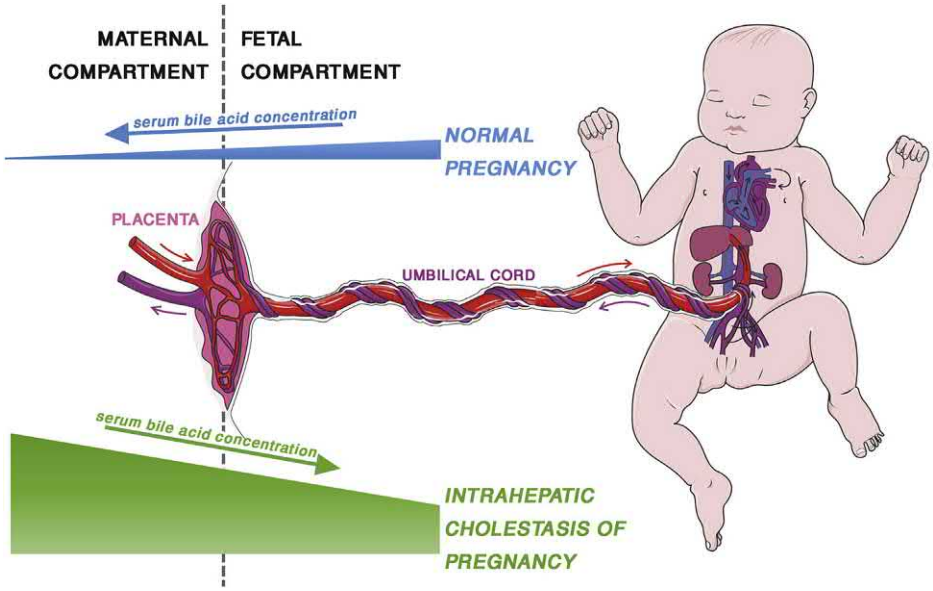

FIGURE 65.1 Schematic representation of the fetomaternal bile acid concentration gradient in normal pregnancies and pregnancies complicated by ICP. In normal pregnancy, the fetus has a slightly elevated TSBA concentration compared with the mother, which leads to the transfer of bile acids via the placenta and subsequent excretion of bile acids by the maternal compartment. In pregnancies that are complicated by ICP, the mother's TSBA concentration elevates to a value higher than that of the fetus, leading to the movement of bile acids from the maternal to the fetal compartment and resulting in a dysfunctional fetomaternal transplacental gradient [6]. UDCA treatment has been shown to reverse this dysfunctional gradient. *ICP*, intrahepatic cholestasis of pregnancy; *TSBA*, total serum bile acid; *UDCA*, ursodeoxycholic acid.

depression between case and control fetuses upon examination of intrapartum ECGs [17]. However, the mean TSBA concentration in the case cohort was 15.9 μmol/L, which is classified as mild ICP, and most participants were UDCA-treated [17].

There has, however, been an overwhelming amount of data that demonstrates ICP changes the physiology of the fetal heart, with one of the most interesting findings being the change in PR interval length. In a cohort of patients with UDCA-treated mild ICP who had a mean TSBA concentration of 28.3 μmol/L, the fetal mechanical PR interval as measured by echocardiography was significantly longer when compared with the control cohort [18]. Although a significant correlation between TSBA concentration and fetal PR interval length was not present, there was an association between the presence of ICP and the elongation of fetal PR interval when confounding factors were removed [18]. A study with an untreated cohort of women diagnosed with ICP also found an elongated fetal mechanical PR interval [19]. TSBA concentrations were not measured in this cohort and ICP was diagnosed by persistent palm and sole pruritus, although all ICP women were stated to have significantly deranged serum concentrations of total bilirubin and transaminases [19]. Multiple linear regression showed that the elongation in PR interval length persisted even after controlling for the liver dysfunction markers that had been measured [19]. An investigation in women with both mild and severe ICP showed a significant association between disease severity and mechanical PR interval length [20]. In vitro investigations into a fetal heart model of ICP PR interval length of whole neonatal rat hearts showed an elongation of PR interval upon perfusion of taurocholic acid (TCA) at a concentration of 400 μmol/L, an effect that was prevented by cotreatment with UDCA [21].

Fetal left ventricular dysfunction in intrahepatic cholestasis of pregnancy

Echocardiography analysis of severe ICP cases has shown evidence of left ventricular dysfunction in fetal hearts of mothers with ICP. Investigation into the fetal-modified myocardial performance index (MPI) showed an increase in isovolumetric contraction and relaxation times [22]. The differences in left ventricular MPI (LMPI) in particular were found to be exacerbated in patients with severe ICP as opposed to mild; the majority of women in this study had not commenced UDCA treatment at the time of measurement [22]. In addition to the increase in LMPI values in ICP, a nonsignificant decrease in E/A ratio has been reported, suggesting further abnormalities in ventricular diastolic function [23]. Contrary to previous data, the LMPI was not affected by severity of ICP; however, investigating the predictive ability of these LMPI values on adverse perinatal outcomes yielded a statistically significant receiver operating characteristic curve [23]. There was no

difference between untreated and UDCA-treated disease cohorts [23]. The aforementioned data are further supported by a more recent study, which found an increased LMPI, isovolumetric contraction, and relaxation times in a larger cohort with a mean TSBA concentration of 39.4 μmol/L and also found a significant correlation between adverse perinatal outcomes and LMPI; all participants in this study had been treated with UDCA [24].

Patients with severe ICP have demonstrated increased fetal diastolic myocardial tissue velocities of the mitral and tricuspid annuli when compared with matched control and mild ICP cohorts, particularly the mean systolic and early and late diastolic motion velocities [25]. The use of UDCA treatment in the disease cohorts was not clarified [25]. Left ventricular global longitudinal strain, diastolic, and systolic strain rates were found to be significantly decreased in patients with ICP, this impairment was associated with severity of ICP [26]. It was not clear whether this cohort has been treated with UDCA [26]. In addition to dysfunctional myocardial deformation, concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in umbilical cord blood were found to be increased in ICP participants, a result that was again associated with severity of ICP [26]. An increase in another marker of cardiac failure, cardiac troponin I (cTnI), has also been found to be significantly higher in a cohort of fetuses of ICP mothers; the mean maternal TSBA concentration in this cohort was 36 μmol/L [27]. Concentrations of fetal cTnI and LMPI values were found to positively correlate with maternal TSBA concentration [27].

Cardiotocograph abnormalities and case reports in intrahepatic cholestasis of pregnancy

There have been numerous investigations indicating ICP-associated abnormalities in cardiotocograph (CTG) tracings during parturition, some of which have preceded fetal demise. According to the National Institute for Health and Care Excellence (NICE) guidelines, a nonreassuring or abnormal CTG is defined by the observation of irregularities in baseline heart rate, baseline heart rate variability, and/or heart rate decelerations and accelerations [28]. Laatikainen et al. first reported the association between the increased occurrence of CTG abnormalities and severe ICP [8]. This finding has since been confirmed in multiple studies, which have reported a higher incidence of fetal distress, abnormal fetal heart rate, and nonreassuring events in intrapartum CTGs in women with ICP [29–31].

Case reports have highlighted fetal arrhythmic activity detected via CTG monitoring and/or echocardiography. One report presented a patient with ICP that had tachydysrhythmia, leading to atrial flutter confirmed by ultrasound; the severity of ICP and usage of UDCA treatment was not stated [32]. Supraventricular tachycardia (SVT) with secondary hydrops fetalis was reported antenatally via echocardiogram in a patient at 28 weeks of gestation; this patient was later diagnosed with mild ICP and the SVT resolved with antiarrhythmic therapy; UDCA treatment was administered to treat the ICP [33]. A similar case was also reported whereby the SVT only resolved after the fetus was delivered, demonstrating that fetuses from pregnancies complicated by ICP can be resistant to antiarrhythmic therapy [34]. Lee et al. have described sudden fetal bradycardia in two cases diagnosed with TSBA concentrations of 79 and 36 μmol/L, respectively [35]. The former case had a sudden prolonged deceleration after the onset of labor, which resulted in fetal demise (Fig. 65 2). The latter case resulted in a live birth; however, prolonged decelerations were observed during labor; UDCA treatment normalized this patient's TSBA concentration prior to labor [35]. Fetal bradycardia has also been reported in a case of a pregnancy complicated by primary sclerosing cholangitis (PSC), which resulted in an extreme elevation of circulating TSBA [36]. One case of a woman diagnosed with severe ICP who had her TSBA concentrations lowered by UDCA treatment reported sudden fetal demise with CTG parameters shown as normal 1 day prior [37]. However, IUD in ICP is not always preceded by CTG abnormalities, typified by one reported case where there was careful antenatal monitoring [8].

Experimental evidence of bile acid–induced cardiac dysfunction

In addition to the above data that have been recorded in humans, there is also substantial in vitro evidence of elevated bile acid concentrations, causing contractile dysfunction in the heart that has been taken from animal models. Early experiments on rats demonstrated that injection of cholic acid (CA) resulted in dose-dependent bradycardia [38]. Negative ionotropic effects were also observed that upon administration of conjugated and deconjugated primary and secondary bile acids on rat, ventricular muscle resulted in a decrease in active tension [39]. The transmembrane action potential in the ventricular myocytes was also found to be reduced, which resulted from a disruption in the movement of inward calcium (Ca^{2+}) and outward potassium (K^{+}) currents [39]. Administration of CA on mice ventricular muscle strips has also been demonstrated to cause a decrease in contractile tension [40]. Perfusion of TCA, the bile acid that is elevated most in ICP, in whole neonatal rat hearts results in slowing conduction velocity at the atrioventricular node, an effect that was attributed to abnormal modulation of t-type calcium channels [21]. Investigations on human atrial

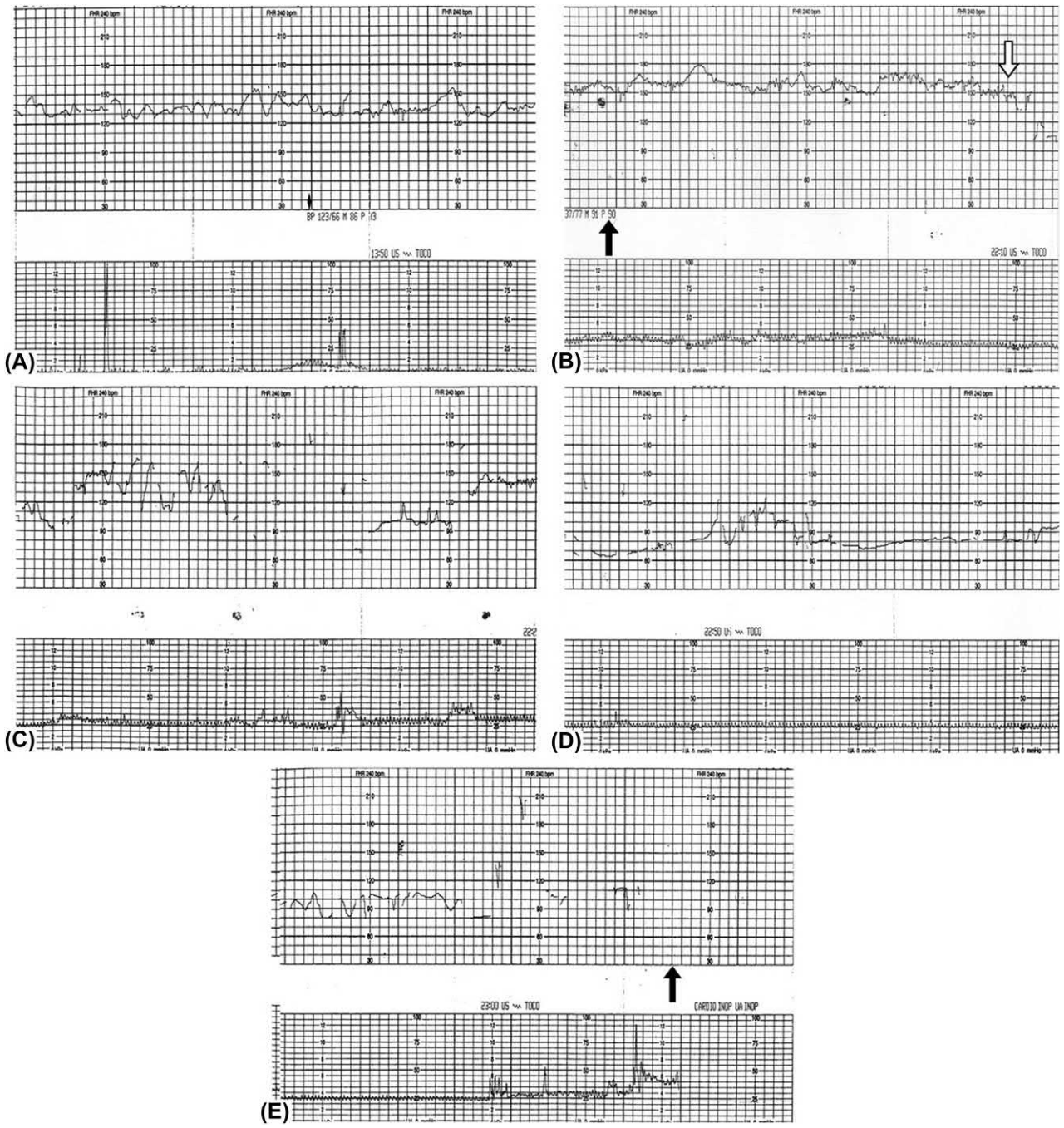

FIGURE 65.2 Cardiotocographic trace displaying the onset of a prolonged fetal heart rate deceleration as reported by Lee et al. [35]. Fetal bradycardia persisted until delivery and resulted in IUD [35].

trabeculae have also shown that conjugated primary bile acids cause a dose-dependent increase in arrhythmic contractions; TCA in particular was the most effective in doing this [41]. Incubation of rat cardiac mitochondria with bile acids caused an induction in mitochondrial permeability transition pore (mPTP) opening, an effect that was more significant for the most hydrophobic bile acids tested [42].

Knocking out bile acid receptors *Fxr* and *Shp* in mice results in cardiac hypertrophy, bradycardia, and elongated PR and QT intervals, an effect that is mimicked upon injection of bile acids into wild-type mice [43]. Moreover, administration of the bile acid sequestering drug cholestyramine resulted in restoration of normal cardiac function in the double knockout mice [43]. Inducing cholestasis in

mice also resulted in bradycardia, hypertrophy, and an increase in ejection fraction and cardiac stress markers [44]. The same group also found "cholecardia" in these models, a term used to describe metabolic dysfunction in hearts subjected to a cholestatic state. A metabolic switch from fatty acid to glucose oxidation was observed based on gene expression studies, suggesting the presence of cardiac stress; this was again reversed by the normalization of circulating bile acid concentrations [43].

Administration of TCA to early versions of a neonatal rat model consisting of a synchronously beating neonatal rat cardiomyocyte monolayer resulted in a dose-dependent reduction in the rate and amplitude of contractions [45]. It is thought the alteration in Ca^{2+} dynamics caused by TCA, and other conjugated bile acids, is mediated via the acetylcholine muscarinic M2 receptor [46,47]. Further evidence from neonatal mouse ventricular cardiomyocytes has shown that conjugated bile acids act partially through the Gi pathway; however, unconjugated bile acids are potent agonists for the bile acid receptor Gpbar1 (Tgr5) [47]. A further developed version of the above model, consisting of coculture of rat neonatal cardiomyocytes and myofibroblasts, has been established to reflect the transient expression of myofibroblasts observed in the fetal heart during the later trimesters of gestation (Fig. 65.3) [48]. Importantly, the TCA-induced dysfunction is not observed in a corresponding cardiomyocyte-only maternal model, which supports the majority of evidence pointing to a fetus-specific cardiac dysfunction observed in ICP [48,49].

Efficacy of ursodeoxycholic acid treatment in intrahepatic cholestasis of pregnancy

As demonstrated by the echocardiography studies investigating LMPI and PR interval, UDCA treatment does not appear to have a protective effect against ICP-induced increase in these parameters. Case reports have also not shown that UDCA improves ICP-induced CTG abnormalities, although this has not been addressed in a prospective study. The PITCHES study, the largest clinical trial thus far investigating the efficacy of UDCA on ICP-associated perinatal outcomes, demonstrated that UDCA treatment in ICP does not have a significant effect in preventing a composite outcome that included all preterm birth (iatrogenic and spontaneous), IUD, and neonatal unit admission [50]. Although 76% of women enrolled onto this trial had mild ICP, a subgroup analysis of only women with serum bile acid concentrations ≥40 μmol/L did not demonstrate a

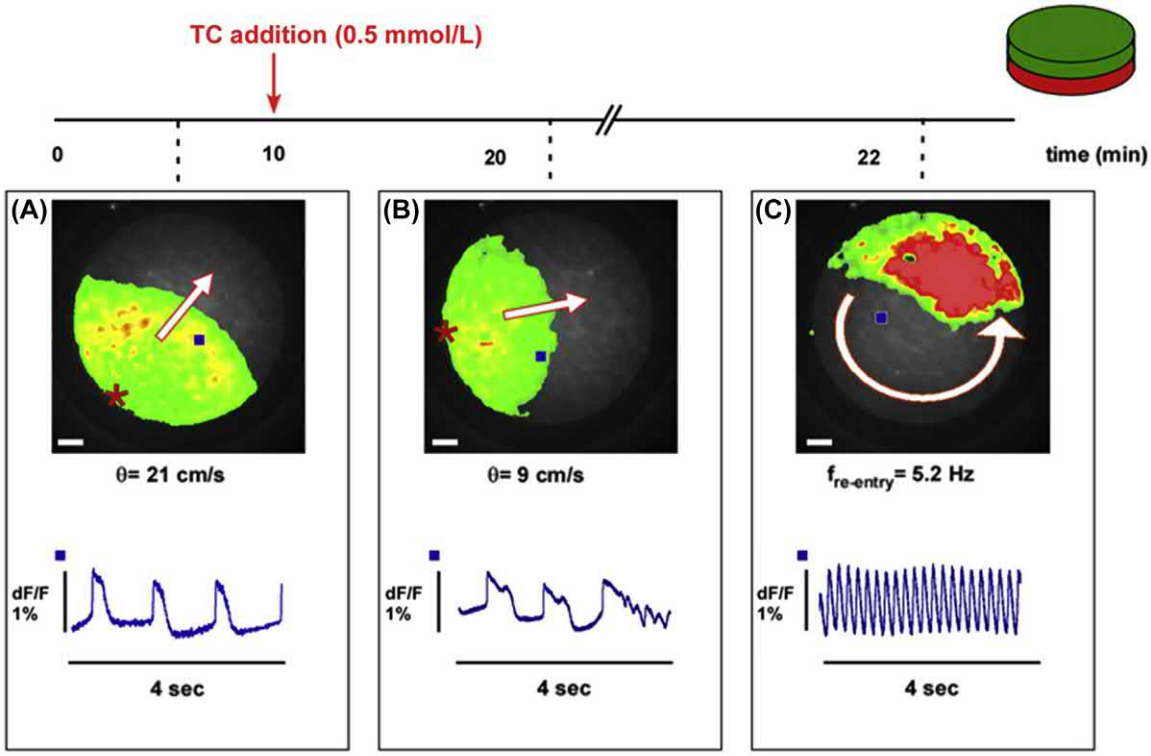

FIGURE 65.3 Optical recording displaying an arrhythmia caused by TCA administration in a fetal heart model consisting of neonatal cardiomyocytes coated with myofibroblasts as described by Miragoli et al. [48]. (A) Spontaneous activity of the fetal heart model with origin and direction of propagation indicated by the asterisk and arrow. (B) Acute administration of TCA results in a decrease in conduction velocity. (C) This is followed by evidence of self-sustained reentrant excitation in the model [48]. *TCA*, taurocholic acid.

difference in the composite outcome between UDCA and placebo treated women [50]. However, the number of women in this trial who had peak TSBA concentrations of >100 μmol/L prior to treatment was low (9 vs. 7 women in each group), which suggests further studies on UDCA treatment are required to form conclusions about this subset of women who are most at risk of an IUD [9,50].

Although in vivo data have not demonstrated a beneficial effect of UDCA in fetal hearts of pregnancies complicated by ICP, very few studies have addressed this question in severe cases, and in vitro models suggest that it has a protective or normalizing effect against TCA-induced dysfunction. Incubation of neonatal rat cardiomyocytes with UDCA attenuated TCA-induced contractile dysfunction and changes in Ca^{2+} dynamics [48]. This was also seen in preparations of human atrial trabeculae exposed to TCA [41]. A protective effect was also observed in TCA-induced slowing of ventricular conduction in perfusions of neonatal rat hearts, an effect that was thought to occur through targeting of developmentally regulated T-type calcium channels [21]. It has been shown that UDCA prevents TCA-induced depolarization of the resting membrane potential of neonatal myofibroblasts but not cardiomyocytes in a fetal heart model consisting of both cell types, an effect thought to be mediated by the sulfonylurea receptor subunits of the K_{ATP} channel [48,49]. Evidence from a neonatal mouse ventricular cardiomyocyte model has shown UDCA to be a potent agonist for Tgr5 expressed in this cell type, although it did not decrease the contraction rate as seen in the aforementioned studies [47]. Other studies suggest that UDCA acts by displacing more hydrophobic bile acids rather than having a direct action on the heart, as demonstrated by UDCA attenuating portal vein stenosis–induced Ca^{2+} influx dysfunction in rat ventricular muscle strips but having no effect on acute exposure of CA to rat papillary muscle [40].

Ursodeoxycholic acid treatment in the absence of intrahepatic cholestasis of pregnancy

In the absence of ICP or elevated hydrophobic bile acids, treatment with UDCA has been shown to be protective against cardiac dysfunction in various animal models of disease.

Historic experiments by Ro et al. demonstrated the ability of UDCA to cease spontaneous and pharmacologically induced arrhythmias in rabbit atria in vitro [51]. UDCA treatment prior to induction of global ischemia and reperfusion injury in isolated rat hearts improved the recovery of myocardial contractility and decreased lactate dehydrogenase [52]. Tauro-conjugated UDCA (TUDCA) can also prevent apoptosis in rats that have had induced myocardial infarction [53]. In mice that have had transverse aortic constriction, administration of TUDCA reduced endoplasmic reticulum (ER) stress markers, myocardial fibrosis, and cardiac hypertrophy [54]. TUDCA administration in mice with abdominal aortic aneurysm resulted in a reduction in the amount of apoptosis markers and ER stress chaperones [55]. In a rat model of $CoCl_2$-induced hypoxia, UDCA inhibited the activation of p53 and HIF-1α; transcription factors that have been implicated in dysregulation of cardiac function in hypoxia [56]. It has also been shown to increase cell viability and reduce the effects of $CoCl_2$-induced hypoxia via upregulation of ERK and PI3K-Akt signaling pathways and inhibition of sphingomyelinases (SMases) in neonatal rat cardiomyocytes [57]. The cytoprotective effects via the PI3k-Akt pathway have also been found in rats with left coronary artery occlusion due to inhibition of mPTP; UDCA was also found to improve postischemic recovery of myocardial ATP content in these rats [58]. Mice with induced myocardial fibrosis had significantly decreased fibrosis, collagen I and III, and TGFβ-1 expression upon administration of UDCA [59]. In mouse models of obesity, TUDCA has been shown to normalize mPTP opening, SERCA2α, and phospholamban activity as well as contractile dysfunction in the heart [60,61]. In the OLETF diabetic model, TUDCA normalized mitochondrial phosphorylation enzymes and the mPTP opening threshold in rat cardiomyocytes [62]. In a study investigating a range of bile acids on rat cardiac mitochondria, glycol-conjugated UDCA was found to be the least toxic and had the least significant effect on mPTP opening and membrane potential [42].

Use of animal models has therefore supported the use of UDCA treatment for cardiac injury caused by myocardial infarction, obesity, and diabetes. In addition to the aforementioned animal experiments, clinical trials investigating UDCA treatment in adults have supported its use in cardiac disease. In a randomized placebo-controlled crossover study of 16 men with chronic heart failure, it was fond that UDCA significantly improved postischemic blood flow in the arm and there was a nonsignificant trend for improvement in the leg [63]. It has also been demonstrated to reduce diastolic blood pressure in healthy participants [64]. A study of 11 patients with coronary heart disease (CHD) demonstrated that UDCA improved endothelium-dependent nitric oxide–independent vasodilation in the arm, a function that is usually decreased in patients with CHD [65]. Moreover, an investigation on patients with atrial fibrillation showed that they have lower levels of conjugated UDCA in their sera [41].

UDCA has also been suggested to attenuate heart transplant rejection. In a retrospective study of cholestatic patients who were receiving cardiac allografts, adjuvant UDCA therapy lowered the number of acute rejection episodes in the first 6 months postsurgery [66]. It has

demonstrated a protection against allograft rejection in murine models without cholestasis; UDCA-treated mice had indefinite survival of mismatched cardiac allografts and increased generation of regulatory T cells, which have a suppressive activity in leukocyte cultures [67]. These outcomes are in agreement with an earlier study on rats that showed UDCA treatment with concomitant antithymocyte globulin (ATG) administration prolongs cardiac allograft survival and increases allograft tolerance [68].

Summary and conclusions

There is overwhelming evidence to suggest that ICP-associated IUD is most likely due to a sudden cardiac arrhythmia caused by elevated serum bile acid concentrations. This hypothesis is supported by studies in humans, which have shown increased fetal heart rate abnormalities in intrapartum CTG recordings, fetal PR interval length, and left ventricular myocardial performance index; this has been shown to be associated with severity of disease and concentration of TSBA. Data from animal models have also demonstrated that hydrophobic bile acids cause cardiac hypertrophy, dysfunctional contractility and cholecardia, and effect thought to be due to bile acids acting as an agonist to muscarinic M2 receptors and causing dysfunctional Ca^{2+} dynamics. UDCA appears to have a protective effect in these animal models, and in vitro and in vivo evidence has suggested it can aid recovery from cardiac injury. However, its usefulness in preventing fetal cardiac dysfunction in pregnancies complicated by ICP has not been proven, although this may be due to a paucity of studies that consider the presence or degree of hypercholanemia and adjust for UDCA treatment. Further studies with larger cohorts are required to establish the efficacy of UDCA on the fetal heart that has been compromised by ICP, the relationship of the bile acid pool and fetal cardiac dysfunction, and the exact mechanism that causes ICP-associated IUD.

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Part XV

Sudden cardiac death

Chapter 66

Sudden cardiac death—epidemiology and demographics

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Sudden cardiac death (SCD) is a major public health issue worldwide. It remains a leading cause of mortality accounting for approximately half of all cardiovascular deaths and 20% of all deaths. SCD is defined as unexpected natural death due to cardiac causes, which occurs within an hour from the onset of symptoms. A longer, 24-h window is frequently used for unwitnessed deaths or deaths that occurred during sleep. In such cases, SCD victims should be known to be alive and functioning normally prior to the event. Preexisting heart disease may or may not have been previously recognized [1,2]. As emphasized by Myerburg, cardiac arrest survivors and postinfarction patients with low ejection fraction are characterized by the highest prevalence of SCD, but the highest absolute number of SCDs occurs in lower-risk subgroups including those with no evident underlying structural pathology [3]. The challenge in SCD risk prediction is, to a large extent, related to its multifactorial etiology involving a complex interplay between genetic predisposition, structural or arrhythmic substrate, and triggers of a final event. Sudden death may result from ventricular tachycardia or fibrillation, bradyarrhythmias, or pulseless electrical activity. Tachyarrhythmias constitute the major final event leading to cardiac arrest accounting for approximately 85% of all cases [4,5]. More recent data based on recordings from implantable loop recorders confirmed that tachyarrhythmias are more frequently associated with sudden deaths, while bradyarrhythmias and electromechanical dissociation are mostly observed in nonsudden and/or noncardiac deaths [6].

Even though last decades saw a significant improvement in primary and secondary prevention of SCD, prediction of such events remains challenging and unsolved [7−9].To underline the importance of SCD, it is emphasized that from the healthcare standpoint, years of potential life lost from sudden death are comparable to those observed in patients with cancers. As documented by Stecker et al. the incidence and premature death burden was higher for SCD than for any individual cancer in men and women and the trend was observed across all age groups. In men <65 years old, calculated years of potential life lost from SCD were twofold higher than from any kind of cancer [10].

Sudden death is estimated to affect between 1 and 4 million patients worldwide annually. The incidence of SCD worldwide has been reported to range usually between 40 and 80 per 100,000 [1,2,11−16]. These numbers are derived mostly from observational studies based on the review of death certificates and relate to data provided according to International Classification of Diseases (ICD-9) codes. As low an incidence as 37 cases per 100,000 was reported in an SCD Study among residents of Southern Okinawa [17]. A similarly low incidence of 41 per 100,000 residents was estimated by Chinese investigators [18]. In general, as shown by a review of prospective studies on out-of-hospital cardiac arrests and following survival rates, SCD rates are the lowest in Asia (52.5 per 100,000) as compared to Europe (86.4 per 100,000), North America (98.1 per 100,000), and Australia (111.9 per 100,000) (Fig. 66.1) [13]. The number of SCDs in the United States has been reported as between 180,000 and 450,000 cases annually depending on the source of data. These numbers correspond to 7%−18% of all deaths in the United States [2,11,12]. EuReCa ONE, an international, European, prospective, multicenter 1-month study, investigated patients who had an out-of-hospital cardiac arrest in October 2014 and who were attended and/or treated by an Emergency Medical. According to this report, 10,682 confirmed out-of-hospital cardiac arrest cases occurred within 1 month in 248 different regions from 27 countries, covering an estimated population of 174 million (34%) out of 514 million people from these European countries [19].

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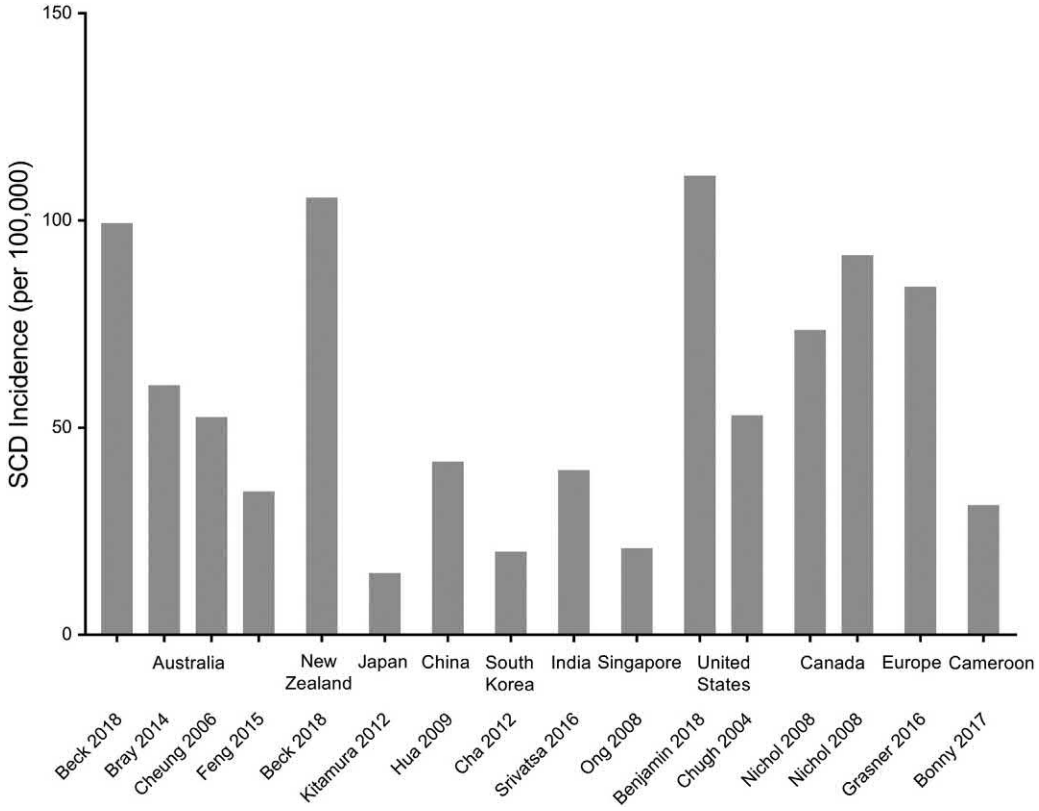

FIGURE 66.1 Global incidence and regional differences in the incidence of sudden cardiac death. *Reproduced with permission from Wong CX, Brown A, Lau DH, Chugh SS, Albert CM, Kalman JM, Sanders P. Epidemiology of sudden cardiac death: global and regional perspectives. Heart Lung Circ 2019;28:6–14.*

SCD usually refers to out-of-hospital events. Nevertheless, as emphasized by a recent review by Andersen et al. the incidence of in-hospital cardiac arrest in the United States is estimated at 250,000 annually and patients who experienced in-hospital cardiac arrest show similar characteristics to out-of-hospital SCA victims (average age 66 vs. 65 years, 60% males for both settings, nonshockable rhythm in 80% of cases). Those who experienced in-hospital cardiac arrest show respiratory and cardiac causes more frequently as compared to presumably cardiac etiology in out-of-hospital setting. Not surprisingly, time to basic and advanced life support is shorter, thus the survival is higher [20].

As shown above, it is difficult to provide the exact and reliable worldwide incidence of SCD. Epidemiology of SCD remains challenging due to differences in definitions of SCD, inconsistency in reporting data, a multifactorial underlying cause of arrhythmias leading to cardiac arrest, and a low rate of autopsy studies and genetic testing. As underlined by some authors, the numbers of SCD events identified based on death certificates are most likely to be overestimated. Not all deaths presumed to be sudden by typical WHO criteria are later proven to be true cardiac deaths on autopsy [21,22]. Prospective analysis of data from Oregon county based on a population of over 600,000 residents showed that retrospective analysis of death certificates overestimated the true SCD rate nearly threefold as compared to the prospective analysis based on data acquired from first responders medical team and autopsy studies. The retrospective death certificate–based review yielded an incidence of 153 in 100,000, while prospective analysis reported an incidence of 53 in 100,000 (5.6% of overall mortality) [21]. Interestingly, as documented by a large database from POST SCD Study (Prospective Countrywide Surveillance and Autopsy Characterization of SCD) which identified all deaths due to out-of-hospital cardiac arrest presumably as SCD that occurred between 2011 and 2014 in San Francisco County, only 55.8% of cases that were considered as sudden by typical clinical criteria were proven to be truly sudden cardiac arrhythmic deaths as identified by autopsy. The incidence of SCD was 29.6 per 100,000 person years, and 69% of SCD cases were males. The incidence rates for WHO-defined SCD and autopsy-defined SCDs were twofold and threefold higher in men as compared to women. Autopsy-defined SCD accounted for 61% of WHO-defined SCDs in men and only for 45% in women. Coronary artery disease was found the most frequent

underlying cardiac abnormality and one-third of coronary patients were found to have acute coronary lesions on autopsy [22].

It is worth emphasizing that the discrepancy in the reported incidence of SCD may not only depend on the differences in definitions used, but it may also reflect a tendency toward declining SCD rate over the last decades, which is believed to be partially attributed to the overall decrease in mortality due to cardiovascular diseases [23–27]. Zheng et al. reported that in 1998 SCD accounted for 63% of all cardiac deaths in adult population aged ≥35 years. As compared to 1989, age-adjusted SCD rate declined by 11.7% in males and 5.8% in females. However, as underlined by the authors, the age-specific increase in SCD rate was observed in middle-aged women (35–44 years old). Fox et al. analyzed temporal trends in mortality including CHD death, nonsudden CHD death, and SCD in the original cohort of Framingham Heart Study and their offsprings comparing four time periods: 1950–69, 1970–79, 1980–89, and 1990–99, with 1950–69 as the reference. The study showed that the risk of SCD was 49% lower in the nineties as compared to 1950–69 period. In patients with a prior history of ischemic heart disease and/or heart failure, the risk was 57% lower than in the referent period, while in those with no prior history of cardiovascular disease, the risk of SCD was 39% lower in 1990–99. The declines in men and women were almost equal [24]. This observation is supported by the data on the temporal trends in out-of-hospital cardiac arrests analyzed within 20-years period between 1979 and 2000 in Seattle. Age- and sex-adjusted incidence of ventricular fibrillation (VF) as a cause of cardiac arrest declined by 56% from 1980 to 2000, while no significant change was observed for asystole and pulseless electrical activity [25]. The decrease in VF incidence was higher in men (57%) than in women (51%). At baseline, VF was observed fourfold more frequently in males than in females, while in 2000, this ratio was estimated to be 3.5-fold higher. Similar observations were reported by more recent data from European centers. Rotterdam Study was designed to evaluate SCD in middle-aged and elderly population. This prospective population-based cohort study enrolled over 14,000 patients aged 45 and older who were followed between 1990 and 2010. During the 20-year follow up, the overall incidence of SCD was 4.2 per 1000 person year, being significantly higher in males than in females (5.2 vs. 3.6 per 1000 persons-year, respectively). The incidence of SCD declined from 4.7 to 2.1 per 1000 persons-year when 1990–2000 and 2001–10 periods were compared [26]. A significant decline in SCD was also reported by Australian investigators. Feng et al. analyzed trends in SCD rates from 1997 to 2010 in adults ≥35 years. A total of 7160 patients aged 35–84 year old were included. Women accounted for 31% of cases were older than male subjects (71 vs. 66 years) and had more frequent history of recent hospitalization due to cardiovascular diseases in the period preceding SCD. A consistent, declining trend in both cardiovascular mortality as well as sudden deaths was observed in the entire population. The average annual decline in age-standardized rate of SCD was higher in women than in men (−4%vs. −2.3% per year, respectively). This fall was parallel to a similar decline in cardiovascular mortality. When this analysis was repeated in subgroups stratified by age (35–54, 55–69, and 70–84), a significant decrease in SCD rates was observed in older patients. Interestingly, no reduction in SCD rate was observed for females from the younger group aged 35–54 years [27].

SCD rates are closely related to age, sex, and the presence of structural or electrical heart diseases. The analysis of all SCD cases reveals two clearly visible age-related peaks: the first one represents mostly sudden infant death syndrome and the second one occurs in elderly people and coincides with an increasing number of coexisting diseases. Coronary artery disease remains the most common condition associated with SCD, and it is reported to be responsible for up to 80% of cases in adult population. The highest risk of sudden death is observed in cardiac arrest survivors, followed by populations of patients with structural heart disease with impaired left ventricular ejection fraction and then by a wide spectrum of patients with other cardiac and noncardiac diseases known to increase the risk of SCD such as diabetes, hypertension, renal diseases, and neurological diseases [1–3,28,29].

Significant sex-related differences in prevalence and clinical manifestation of SCD have been reported. The majority of epidemiological studies have shown a considerably lower rate of SCD in females as compared to males, even if adjusted for conventional cardiovascular risk factors [1,2,28–30]. It is estimated that the annual rate of SCD is only 50% of the one reported in male population. In general, data suggest that women have three to fourfold lower risk of SCD than men. A large cohort from Framingham study showed that women with coronary heart disease had 25% lower risk of SCD than men. Age-adjusted annual rate was 4.6 per 1000 in women and 17.5 per 1000 in men [30]. Recently published analysis by Bogle et al. with very–long-term follow up of Framingham cohort, showed that at the age of 45 years, the lifetime risk of SCD was 10.9% in males versus 2.8% in females [31]. In most reports, the percentage of female subjects among cardiac arrest and/or SCD victims is estimated between 30% and 45%. The incidence of SCD increases significantly with age in both sexes; nevertheless, as documented by several studies, SCD events occur relatively later, even by 10–20 years, in women as compared to men [21,32]. The major difference in SCD incidence is observed in the age

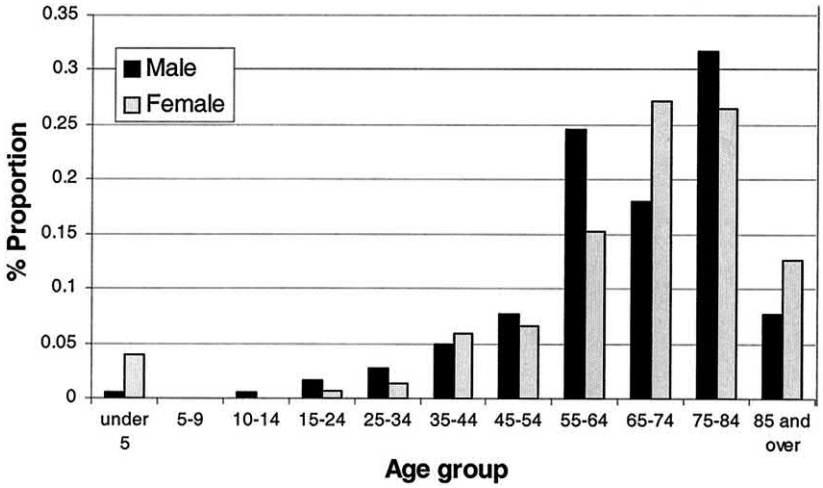

FIGURE 66.2 Sex and age-based composition of prospectively determined sudden cardiac death cohort. *Reproduced with permission from Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, Ilias N, Vickers C, Dogra V, Daya M, Kron J, Zheng ZJ, Mensah G, McAnulty J.Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol 2004;44:1268–1275.*

group of 55–65 years old (Fig. 66.2) [21]. This age-related gender difference in SCD incidence is also parallel to the incidence of ischemic heart disease. Differences in SCD incidence between males and females are observed mostly in middle-aged population, particularly in premenopausal women who are believed to be protected from cardiovascular diseases by hormones. As reported by Zheng et al. no difference in SCD rates was observed at age $\geq$85 years [23]. Ischemic heart disease as the cause of death has been steadily declining over the last decades. Interesting data regarding temporal trends in SCD were provided by Fingersture study that evaluated SCD cases over the last 20 years in Finland. The authors observed that the proportion of ischemic SCDs decreased from 78.8% to 73.4% over the last two decades in both sexes; however, women experienced an increase in the overall number of non-ischemic deaths [33].

Differences in the incidence of SCD depend on ethnicity. Afro-Americans have been reported to show significantly higher rates of SCD as well as poorer survival rates as compared to Caucasian, Hispanics, or Asians [1,2,34,35]. Oregon Sudden Unexpected Death Study (Ore-Suds) showed that age-adjusted SCD rates were twice as high in black men and women as in white men and women (175 vs. 84 and 90 vs. 40 per 100,000, respectively, for males and females) [35] However, black and white study subjects differed in clinical presentation with blacks being younger and more frequently suffering from diabetes, hypertension, and chronic renal failure. This significant difference in ethnicity among SCD victims is particularly emphasized in studies analyzing sudden deaths in young competitive athletes [36,37]. The US Registry of Sudden Death in athletes reported a 6.5-fold higher incidence of SCD in male versus female athletes with almost 5-fold higher incidence of SCD in Afro-Americans [37].

Female victims of SCD are known to show structural heart disease as the underlying cause of cardiac arrest less frequently. Ore-Suds is an ongoing study designed to evaluate SCD cases in Portland area covering approximately 1 million inhabitants. Among 1568 adult victims of SCD identified between 2002 and 2007, 36% were females. Regarding clinical characteristics, females were significantly older (71 vs. 65 years, $P < .001$) and less frequently showed past history of recognized coronary artery disease and/or severe left ventricular dysfunction. However, no differences were observed in respect to prevalence of obesity, dyslipidemia, left ventricular hypertrophy, or prior myocardial infarction [38]. On the other hand, one cannot exclude that lower prevalence of coronary artery disease in women may be partially related to the fact that women present with less symptomatic CAD and therefore they are less frequently diagnosed with CAD before SCD event. Results from autopsy studies provide the most reliable data on underlying etiology of SCD and thus on sex differences in cardiac arrest victims. Recently published data based on a large Finish cohort of nearly 6000 SCD victims, with clinical and autopsy data available, evaluated clinical, morphological, and ECG patterns specific for women and predictive of SCD [33]. The Fingersture study was designed to collect clinical and autopsy data of SCD victims between 1998 and 2017, and it defined SCD as either a witnessed event within 6 h from the onset of symptoms or as unwitnessed death within the 24 h when a subject was last seen alive. As in all previous reports, SCD incidence was significantly higher in males (79%) and ischemic heart disease as the underlying cause

accounted for over 70% of all cases. With respect to the observed sex-specific differences, women were older (70 vs. 63 years old) and characterized by higher BMI values and more abdominal fat. Regarding the causes of death identified by clinical and autopsy data, ischemic and alcoholic cardiomyopathy was identified less frequently in women. On the other hand, females were identified as the sex with a significantly higher prevalence of nonischemic causes such as primary myocardial fibrosis, valvular heart disease, myocarditis, and ARVD. The autopsy showed significant differences in fibrosis between male and female hearts. Even though the absolute percentage of subjects with any degree of fibrosis detected on autopsy, as well as the number of patients with substantial fibrosis, was significantly higher in males (92.4 vs. 89.3 and 12.7 vs. 7.8%, respectively, $P < .001$ for both), females more frequently demonstrated primary fibrosis, defined as interstitial, diffuse, or patchy fibrosis without left ventricular hypertrophy, myocardial scarring, or other causes of fibrosis as the only pathological findings. This diagnosis accounted for 5% of cases in females as compared to 2.6% in males ($P < .001$). Figersture study provided additional data on ECG predictors. ECG tracings available in nearly 20% of studied population showed a significantly higher percentage of abnormal ECGs (at least one ECG abnormality present) in males than in females (84.7 vs. 72.8%, $P < .001$). Wider QRS duration, fragmented QRS, and Q waves were more frequently observed in males, whereas women more frequently displayed LVH criteria (18 vs. 11%), including LVH with secondary repolarization changes. These differences were independent of ischemic versus nonischemic etiology. It is noteworthy that, as in previously published reports, a higher percentage of normal hearts on autopsy or, in other words, a higher prevalence of unexplained SCDs is recorded in women. Cardiac pathologic findings reveal a high rate of SCD of undetermined etiology in younger women. In that large contemporary cohort, the frequency of normal autopsy examination results was found to be threefold higher in females than in males [38]. Another large European database on autopsy studies was published by Naneix et al. [39]. In the French cohort of 534 cases at mean age of 44 years (18−89 range), male to female ratio was 2.24:1 (69 vs. 31%). Cardiovascular causes accounted for 66% of cases with coronary artery disease as the most frequent underlying heart disease. The study reported that cardiovascular diseases were more frequently observed in males irrespectful of the age range, while neurological and pulmonary diseases were more frequently recorded in women.

Current guidelines for primary prevention with implantable cardioverter defibrillator take into account only impaired left ventricular ejection fraction as a sole risk indicator. Nevertheless, as shown by decades of clinical experience, such risk stratification is far from being optimal [1,2]. Several risk models based on clinical, ECG, imaging, and biochemical data are under investigation to improve the process of population and individual risk stratification. Sex is considered as one of the most commonly used risk factors in all SCD risk stratification scales. In overall population, SCD risk factors represent the same group of traditional risk markers considered as factors associated with high risk of developing ischemic heart disease such as age, male sex, hypertension, diabetes, smoking, hyperlipidemia, and obesity. Data on sex-specific clinical risk factors of SCD are limited. It is unknown whether women present with the same risk factors of SCD as men. Studies targeted at an evaluation of SCD risk factors in females such as Nurses' Health Study and Women's Ischemia Syndrome Evaluation showed that smoking, diabetes, inactivity, and overweight played as similar a role as is reported in general population of coronary patients [40,41].

Significant sex differences do not only exist in etiology of SCD but also in clinical presentation of cardiac arrest. Regarding clinical presentation, women more frequently present with asymptomatic coronary artery disease. Consequently, females are less likely to be diagnosed with coronary artery disease before SCD event and more frequently die suddenly due to ischemic heart disease without preceding symptoms [12,16,29,42]. Metaanalysis of survival after sudden cardiac arrest that encompassed over 400,000 patients from the studies including subjects between 1990 and 2010 focused on sex differences and showed that women more frequently experienced sudden cardiac arrest at home, were less likely to have witnessed SCA, and had a lower frequency of shockable rhythm. Nevertheless, their survival at hospital discharge was higher than in male subjects. The authors concluded that the paradox of better survival despite worse prognostic factors indicates that classical prognostic factors may not be the same and may play a lesser role in females [43]. In summary, despite older age at the time of SCD, less frequent prior diagnosis of heart disease and less frequent symptoms preceding cardiac arrest, more frequent nonshockable rhythm, and subsequently lower survival rate, females are compared to males in most analyses on SCD. Consequently, the different risk profile may potentially lead to women actually being less frequently qualified for ICD implantation [44,45]. Furthermore, the available data on sex differences are still limited as women remain underrepresented in clinical trials and guidelines are based mostly on extrapolation of the results of the studies which involve mostly male populations.

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Chapter 67

Sudden infant death and electrophysiology abnormalities in young children

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Sudden infant death

Sudden infant death syndrome (SIDS) is the sudden death of an infant under the age of 1 year with no clear etiology after a careful and thorough case evaluation, including review of the clinical history, death scene, and complete autopsy [1]. Most cases of SIDS, approximately 90%, occur in the first 6 months of life, with peak incidence in the 2−4 month age range, and decreasing incidence thereafter [2]. It is the leading cause of infant mortality in developed countries [1,3] with typically no symptoms prior to the event (Fig. 67.1). SIDS incidence in the United States has declined following the modification of risk factors and recently has plateaued at 53/100,000 [4].

Risk factors for SIDS: Males are more likely to die from SIDS than their female counterparts in a 3:2 ratio. Additionally, there are racial and ethnic groups at higher risk for SIDS, such as Native American/Alaskan and African American [3]. These infants are twice as likely to experience SIDS events as compared to non-Hispanic white infants, Hispanic infants, or Asian/Pacific Islander infants [3].

Pathogenesis of SIDS: The triple risk hypothesis describes the presence of three risk factors that, if present, can predispose a baby to SIDS. These risk factors include (a) environmental triggers, (b) a critical developmental period, and (c) an underlying vulnerability. Environmental triggers include any circumstances that increase the infantile risk for asphyxia, sleeping in the prone position, or side position. The critical developmental period relates to the infantile autonomic system and maturational changes that occur often within the first year of life. Lastly, underlying vulnerability includes genetic and nongenetic susceptibilities. When these factors overlap, the risk is highest.

Cardiovascular contribution: Cardiovascular contributors to SIDS include inherited arrhythmia syndromes (IASs), structural heart disease, and cardiomyopathies [5−7]. The main IASs implicated in SIDS include long-QT syndrome (LQTS) , Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and short-QT syndrome (SQTS). Certain cardiomyopathies may have an electrophysiologic association, such as tachycardia-induced cardiomyopathies, or dilated cardiomyopathy associated with congenital complete heart block. In this chapter, we will explore the electrophysiologic links to SIDS and to other major causes of morbidity and mortality in infants and young children along with the sex-based predispositions to these events.

Inherited arrhythmia syndromes

LQTS: The LQTS is characterized by a prolonged corrected QT interval on electrocardiogram and increased risk of torsades de pointes [8] with a prevalence of 1/2000 live births [9]. LQTS disease−causing mutations were identified in 43% of infants presenting with a QTc ≥470msec and in 29% of the infants with a QTc ≥460 msec [10]. Alterations in potassium handling (loss of function mutations in the main potassium rectifier currents I_{ks} and I_{kr} resulting in the LQTS type 1 and type 2 phenotype) and sodium handling (gain of function in SCN5A resulting in the LQTS type 3 phenotype) account for >75% of patients with LQTS [8,11,12]. Male infants with LQTS type 3 represent the highest risk group of patients and may present

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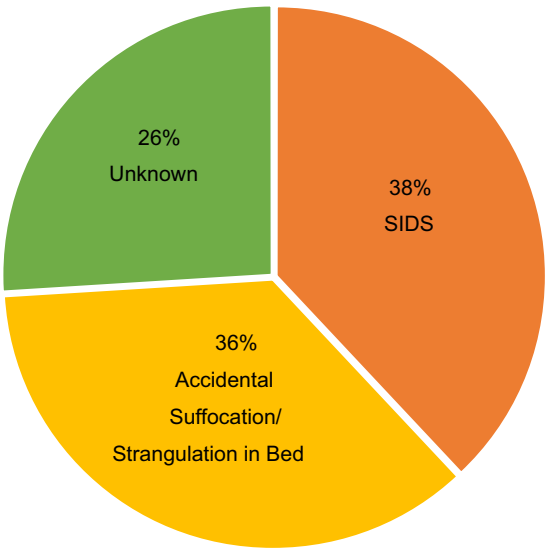

FIGURE 67.1 Pie Chart of the causes of sudden unexplained infant death by cause from 2017. *These data have been adapted from the Center for Disease Control and Prevention website.*

with SIDS as the primary manifestation of the disease in 10%−15% of patients [8]. This sex disparity reverses as the infants mature into childhood and adulthood with females then having greater risk of cardiac events.

For those newborns who have a cardiac event in the first year of life, their prognosis is quite poor [13]. Specifically, for those infants who have an aborted cardiac event in the first year of life, they have an associated hazard ratio of 23.4 for repeat cardiac events or sudden cardiac death during ages 1−10 years. Additionally, in cases of quite severe QT prolongation in infants with LQTS, these infants may present a functional 2:1 atrioventricular block (see Fig. 67.2). Aggressive therapy for these patients has dramatically improved the prognosis for these patients [14].

Treatment: Beta-blockers are first line therapy in LQTS, though they may not always be as effective in young patients. Sodium channel blockers, such as lidocaine and mexiletine, have been used cautiously in patients with LQTS type 3 (see Fig. 67.3). For those infants who survive a cardiac arrest, an automatic implantable cardioverter defibrillator (AICD) can be considered, though the risk benefit ratio of placing such a device in a small patient must be carefully considered. Alternative therapies include pacemakers [15] and left cardiac sympathetic denervation [16−19].

BrS: This is characterized by atypical findings of ST segment elevations in the right precordial leads (predominantly V1 and V2) as well as presence of ventricular arrhythmias and an increased risk of sudden death without an overt structural cause. ECG findings are characterized as "type 1" or ≥2 mm coved ST segment elevation in one or more of the right precordial leads [8]. This pattern may be spontaneous or provoked with the use of a Na^+ channel blocker, such as ajmaline or flecainide [20]. BrS prevalence is estimated to be 1/500−2000 individuals with increased prevalence in Southeast Asia [21], with a well-described male predominance. Additionally, sleeping (with associated high vagal tone) and fever are triggers for ventricular arrhythmias in people with BrS [22]. (see Fig. 67.4). Typically, arrhythmias associated with BrS are typically manifested in the 4th decade of life. However, SIDS infants

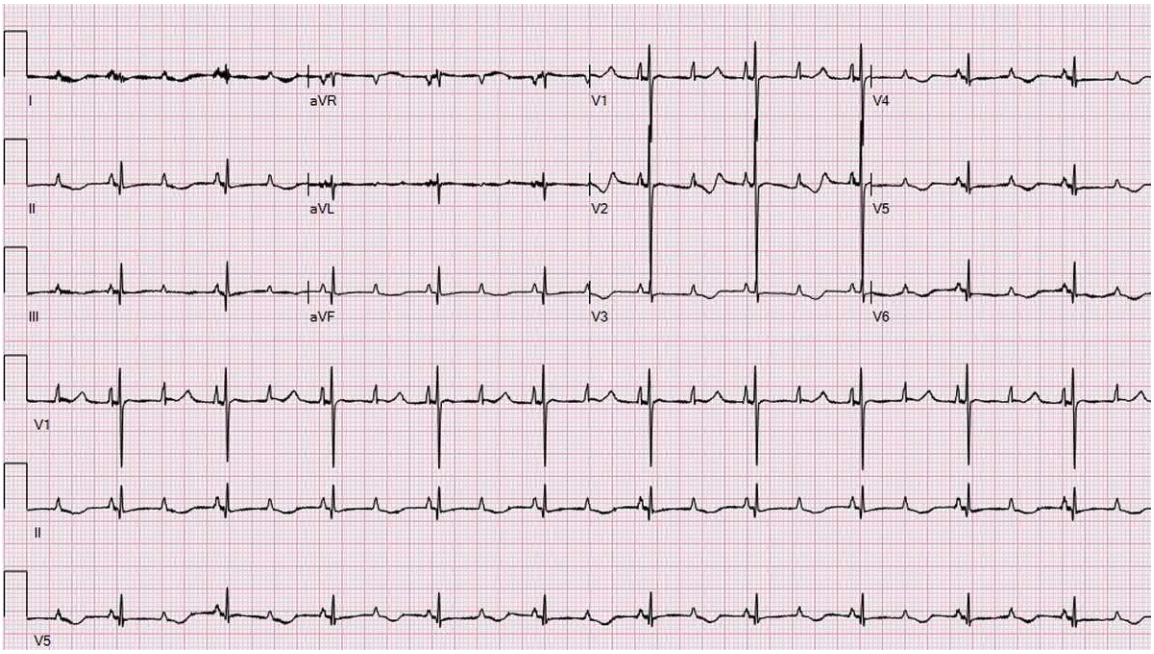

FIGURE 67.2 This 12-lead ECG in a male infant with Long-QT Syndrome demonstrating 2:1 AV conduction and a markedly prolonged QT interval and a QTc of 690 msec? Note the diffusely abnormal T-wave morphology throughout all leads.

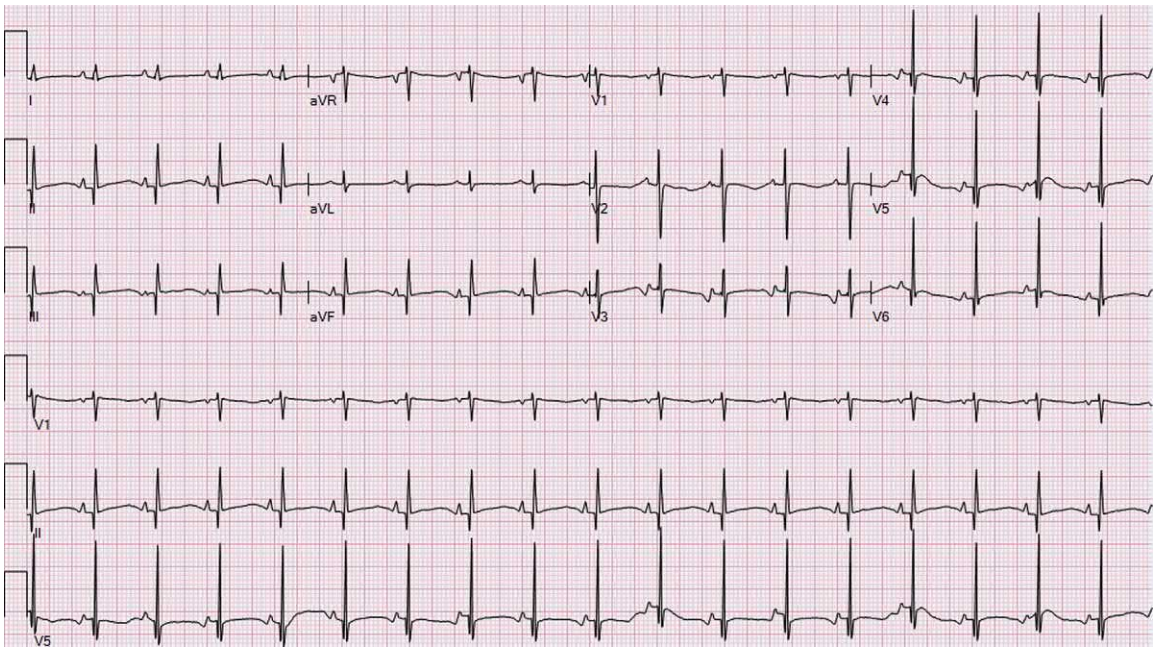

FIGURE 67.3 This 12-lead ECG is from the same patient presented in Fig. 67.2. This ECG is taken after the initiation of intravenous lidocaine. With this medication, the QT shortens to 580msec and now there is resumption of 1:1 AV conduction. The abnormal T waves persist in this exam.

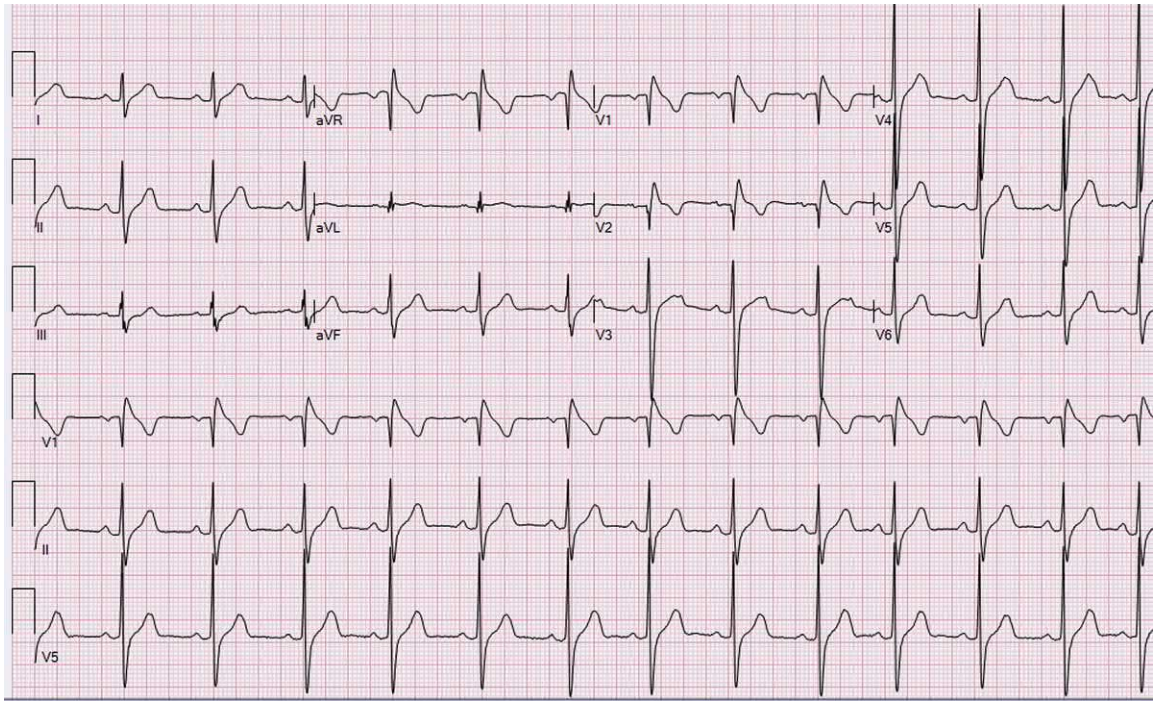

FIGURE 67.4 A 12-lead ECG from a young male who presented to the Emergency Room with fever and palpitations. This patient had a history of atrial flutter and a family history of a male brother having a resuscitated cardiac arrest. This ECG demonstrates a type 1 Brugada pattern (note the ST segment elevation and coved ST segments in leads V1 and V2).

who have been later identified as having BrS have been documented. Priori et al. published a case series regarding a family who had four children who died after unexplained sudden cardiac arrests, with two of the infants presenting at ≤12 months (one male, one female infant) and the remaining two children presenting between the ages of 14−36 months (1 male at 14 months, one female at 3 years) [23]. Interestingly, the fifth young child in this familial cohort was a female who presented with ventricular fibrillation at age 3 and was successfully resuscitated—this child did not carry the BrS familial mutation. This single familial cohort shows the complexity of the IAS in SIDS.

Treatment: Treatment for BrS includes lifestyle modifications (including avoidance of medications that may aggravate the condition, aggressive antipyretic use during febrile illnesses) and AICD implantation where appropriate. Medications, such as quinidine, can be a useful adjunctive therapy. Lastly, catheter ablation may be considered in patients with electrical storm or repetitive appropriate ICD shocks.

CPVT: This is characterized by bidirectional or polymorphic ventricular tachycardia (see Figs. 67.5−67.7) that is often stress or exercise induced and is much less common than LQTS or BrS with an estimated prevalence of 1/10,000 individuals. Mishandling of calcium accounts for 50%−65% of patients with CPVT, with mutations in RYR2 and CASQ2 most commonly seen in genotype-positive patients [11]. CPVT predominantly affects children and has a mortality of 50% in untreated individuals <20 years of age and has been implicated in SIDS [8,24]. It has been demonstrated that genotype-positive RYR2 young males have a higher risk for cardiac events than young females [25,26]. Data from large molecular autopsy case series have shown a prevalence of 12%−14% of infants having mutations in RYR2 [27,28].

Treatment: Treatment for patients with CPVT includes lifestyle modifications (including limiting sports/strenuous activities) as well as beta-blockers and/or flecainide. AICDs and left cardiac sympathetic denervation may be indicated in medically refractory cases. Again, use of devices must be carefully discussed with families prior to implant.

SQTS: The SQTS is a very rare IAS and characterized by a short-corrected QT interval (≤330 msec; or <360msec with one or more of the following: known genetic mutation, family history of SQTS, family history of sudden cardiac death at age ≤40 years, resuscitated ventricular tachycardia/ventricular fibrillation episode of unknown cause). Mutations in the main potassium rectifier currents (gain of function; opposite of the LQTS mutations) have been implicated, as have mutations in L-type calcium channels [29]. Brugada et al. in 2004 described three families with SQTS—from this cohort, in one family there were two male infants who expressed severe phenotypes. One infant suffered an aborted sudden death at age 8 months with severe resultant neurological damage; the 3-month-old brother died suddenly and was diagnosed as having SIDS [30].

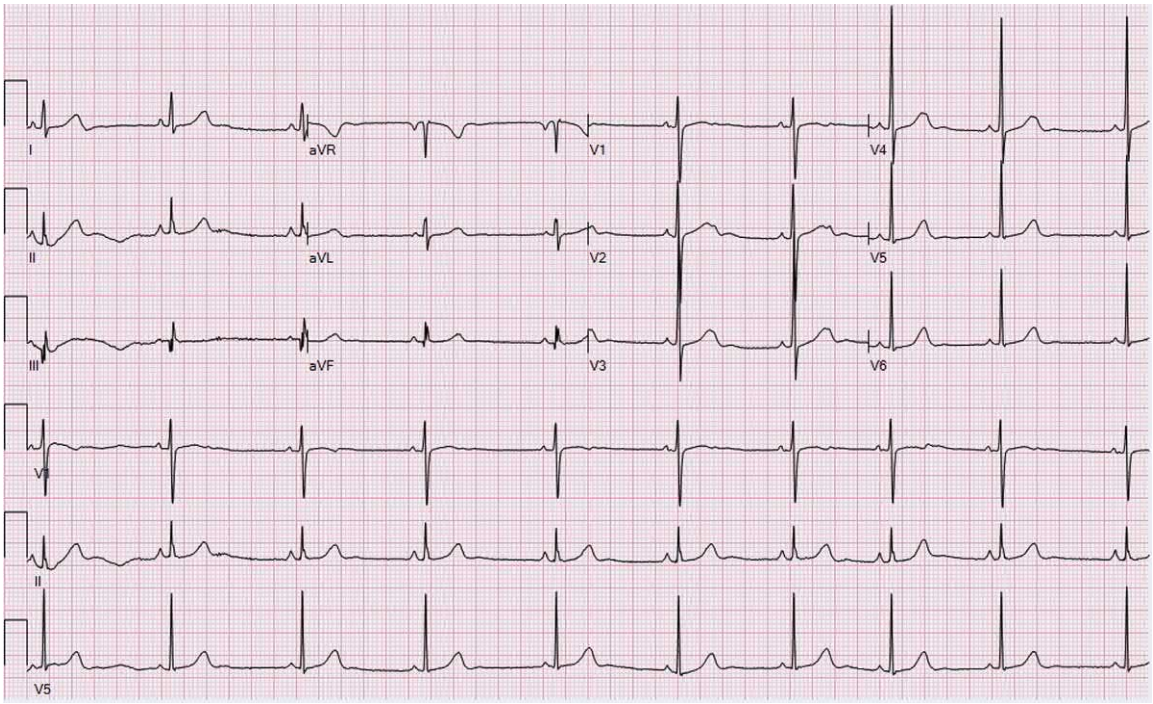

FIGURE 67.5 A 12-lead ECG in a male patient with catecholaminergic polymorphic ventricular tachycardia. Note the normal exam.

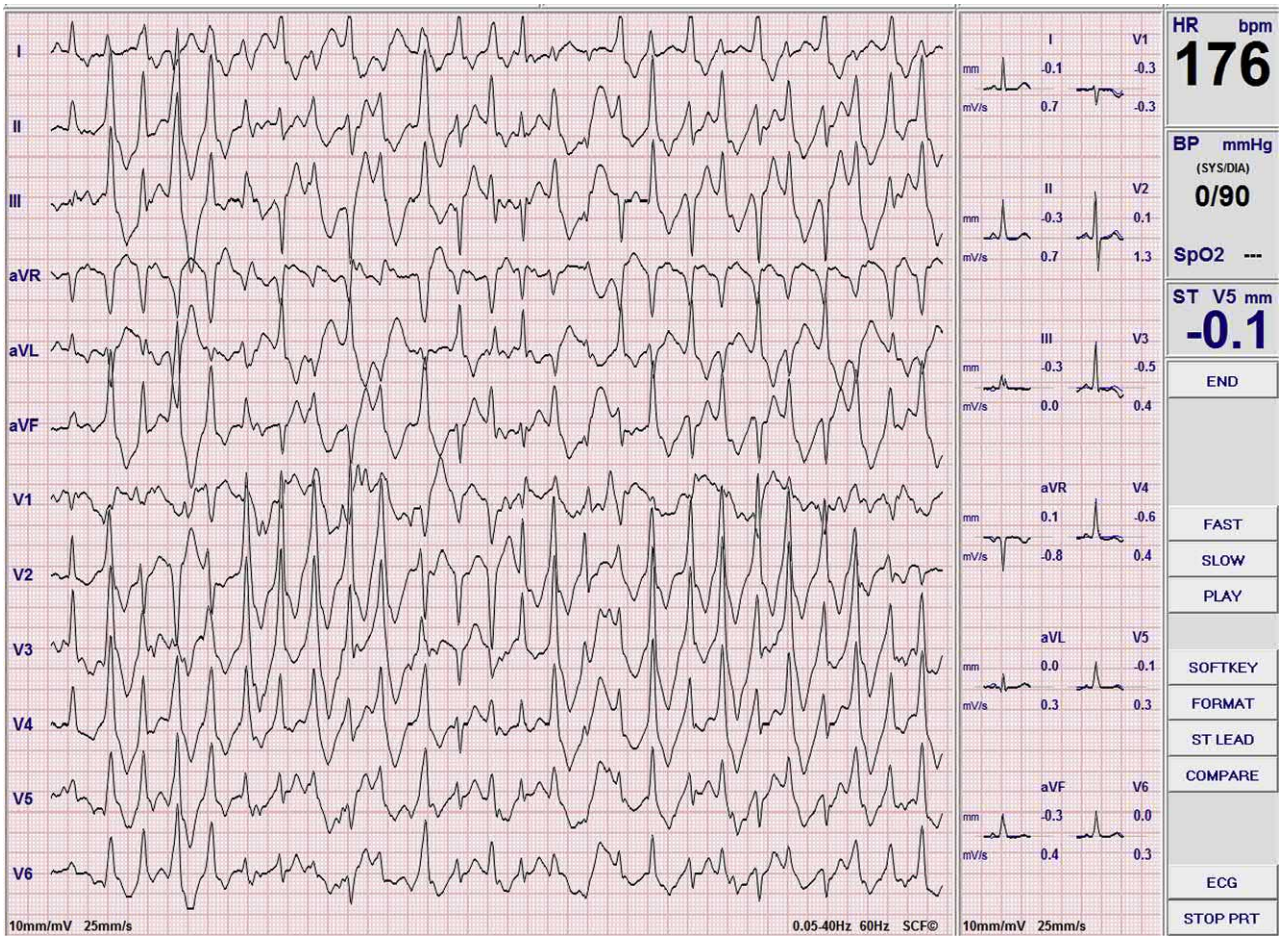

FIGURE 67.6 This is a snapshot of the same male patient from Fig. 67.5. This tracing, taken 1 min and 11 s into an exercise stress test (Bruce Treadmill Protocol), demonstrates bidirectional ventricular tachycardia at a rate of 175 b/min.

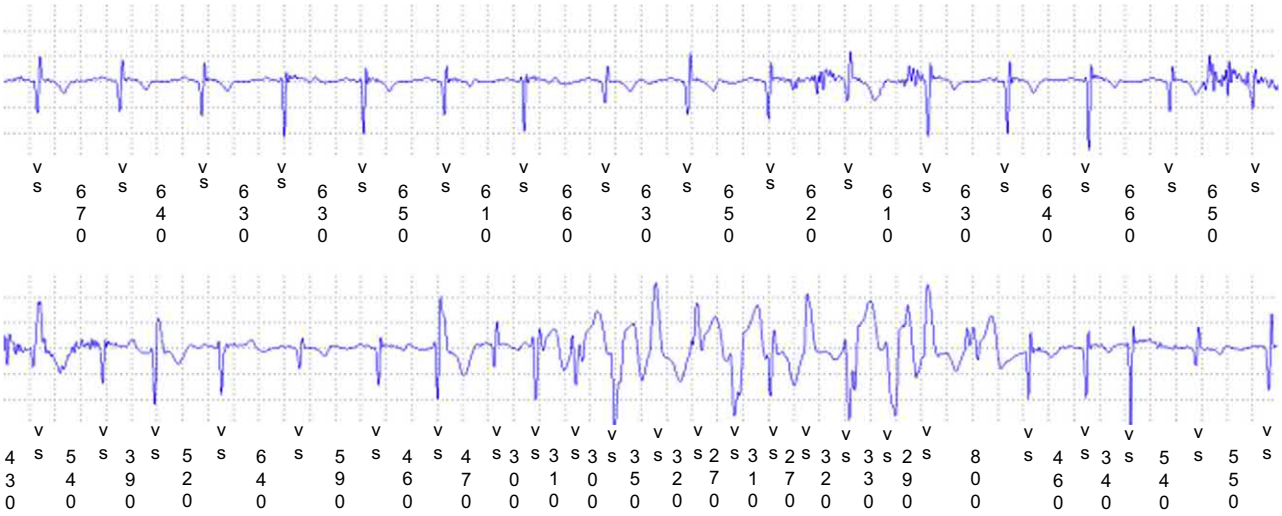

FIGURE 67.7 This is a tracing from an implantable loop recorder in a male patient with genotype-positive catecholaminergic polymorphic ventricular tachycardia and concerning syncopal episodes. The tracing demonstrates nonsustained polymorphic ventricular tachycardia. The event was interestingly not correlated with a symptom but rather was automatically recorded for meeting requirements of the autorecord tachycardia zone.

Treatment: Treatments for SQTS are quite limited to device therapy (predominantly AICD) though medications may be used in certain asymptomatic patients [8].

Clinical implications for families: The 2013 Expert Consensus Statement on Inherited Primary Arrhythmia Syndromes [8] recommends a personal/family history and circumstances of the sudden death are collected for all victims of sudden unexplained death in infancy, in addition to the collection of blood and/or suitable tissue for molecular autopsy (Class I recommendation). Also, an arrhythmia syndrome—focused molecular autopsy/post-mortem genetic test can be useful for victims (Class II recommendation) and can lead to appropriate cascade genetic screening for the first-degree relatives whenever a pathogenic mutation associated with increased risk for sudden death is identified in the index case (Class I recommendation).

This can be helpful for families to identify other potential "at-risk" family members. Additionally, family members identified through cascade screening who may be asymptomatic, genotype positive, and phenotype negative should not be considered unaffected due to the variable penetrance of these IAS.

Given the mediocre diagnostic yield of genetic testing (variable by condition), families should be appropriately counseled regarding the implications of a negative test.

Additional electrophysiologic abnormalities in young children

There are additionally electrophysiologic substrates that can present in infancy, which may have a significant impact on infant morbidity and mortality. These arrhythmias can be categorized into bradyarrhythmias and tachyarrhythmias (atrial, junctional, and ventricular). In this section, we will explore these electrophysiologic abnormalities and sex prevalence.

Bradyarrhythmias

Complete congenital heart block (CCHB): CCHB is defined as atrioventricular block identified within the first month of life. The incidence of congenital heart block is approximately 1 in 22,000 live births [31] with equal numbers of males and females [32]. It is often associated with the transplacental crossing of maternal anti-Ro/SSA or anti-La/SSB antibodies in autoimmune conditions such as systemic lupus erythematosus but can also be present in patients with congenital heart disease.

Congenital heart block can be diagnosed during the prenatal period by fetal echocardiography (see Fig. 67.8). Often, persistent fetal bradycardia is often the inciting diagnosis, bringing these fetuses for pediatric cardiology evaluation. Postnatal diagnosis of completed congenital heart block can be made by an electrocardiogram (see Fig. 67.9). Fetal and neonatal mortality in congenital heart block has been reported as high as 43% and 6%, respectively [33]. Infants with fetal hydrops tend to have the worst clinical outcomes [34].

As many as 50% of patients with congenital heart block may have associated congenital heart disease and should have an echocardiographic evaluation [31]. Commonly associated congenital heart diseases include left isomerism, congenitally corrected transposition of the great arteries, atrial septal defects associated with NKX2.5 mutations, and atrioventricular septal defects [35,36] (see Fig. 67.10). Heart block diagnosed later in childhood may be due to an inherited channelopathies resulting in progressive cardiac conduction disease [37]. Genetic testing for mutations such as KCNK17, NKX2.5, and Tbx5 in families with a strong family history of heart block is recommended.

Treatment: Prenatal treatment for CCHB remains controversial with certain centers advocating for use of steroids; recent data suggest that there is no benefit in steroid administration once complete heart block is present [38,39]. Postnatal pacemaker therapy is the treatment of choice for symptomatic patients [40] including "advanced second or third degree AV block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output." The guidelines further detail a Class I indication for pacing in infants with congenital heart block and a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction and in infants with CHB and ventricular rate less than 55bpm in a structurally normal heart or $<$ 70bpm in patients with congenital heart disease.

Tachyarrhythmias

Supraventricular tachycardias: The incidence of supraventricular tachycardias (SVT) in pediatrics is approximately 1:250 to 1:1000 children with a male predominance in all subtypes of SVT (including atrioventricular reentrant tachycardia, atrial tachycardia [AT], and other SVT subtypes including atrial fibrillation, atrial flutter, and junctional tachycardia [JT]) except for atrioventricular

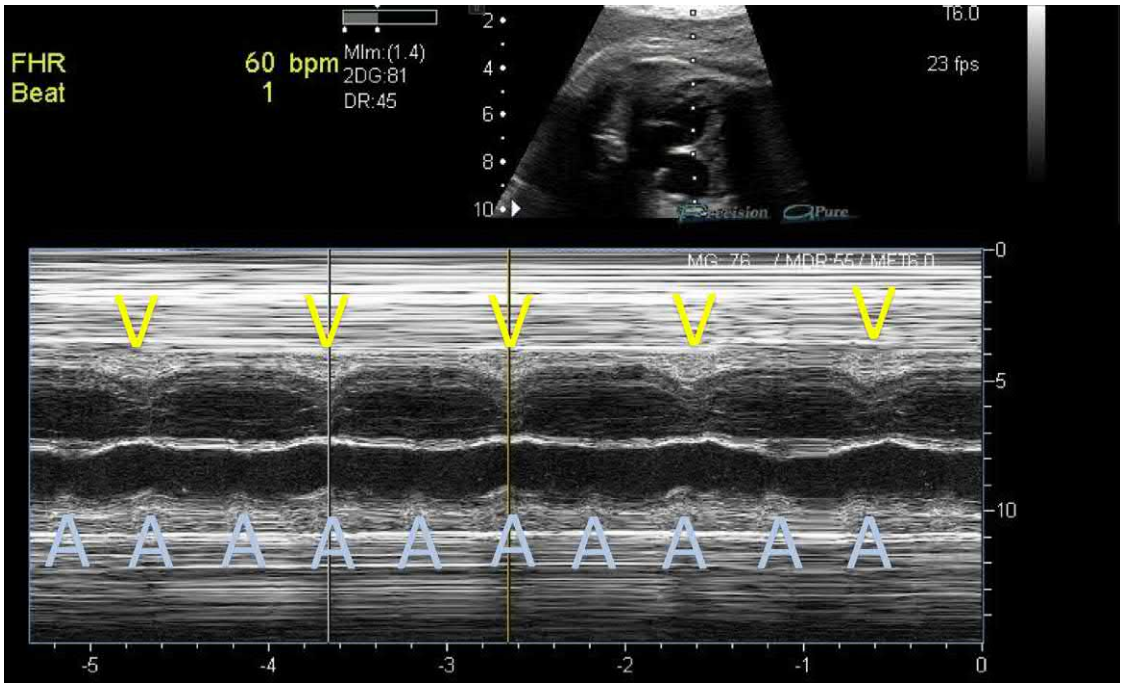

FIGURE 67.8 This is an m-mode fetal echocardiogram from a fetus with complete congenital heart block. The fetal ventricular rate is 60 beats per minute. In the tracing, the ventricular rate is demonstrated by the yellow "V" and the atrial contractions by the blue "A."

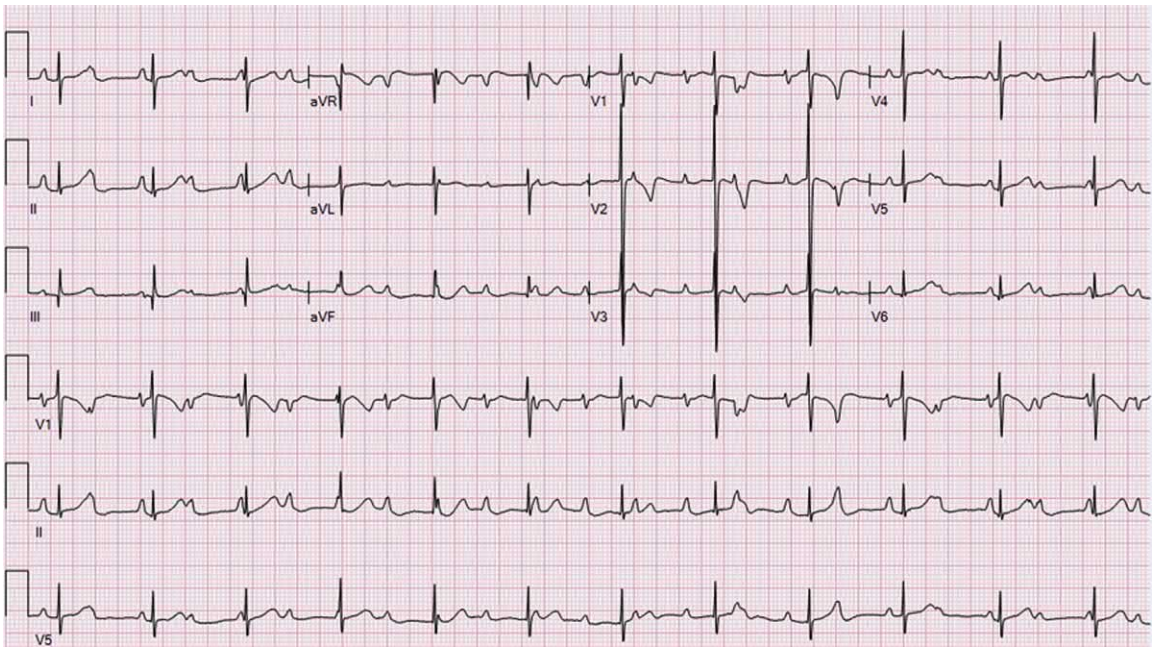

FIGURE 67.9 This is a 12-lead ECG from a female infant with complete congenital heart block. She has an atrial rate of 120 beats per minute and a narrow QRS complex junctional rate of 70 beats per minute.

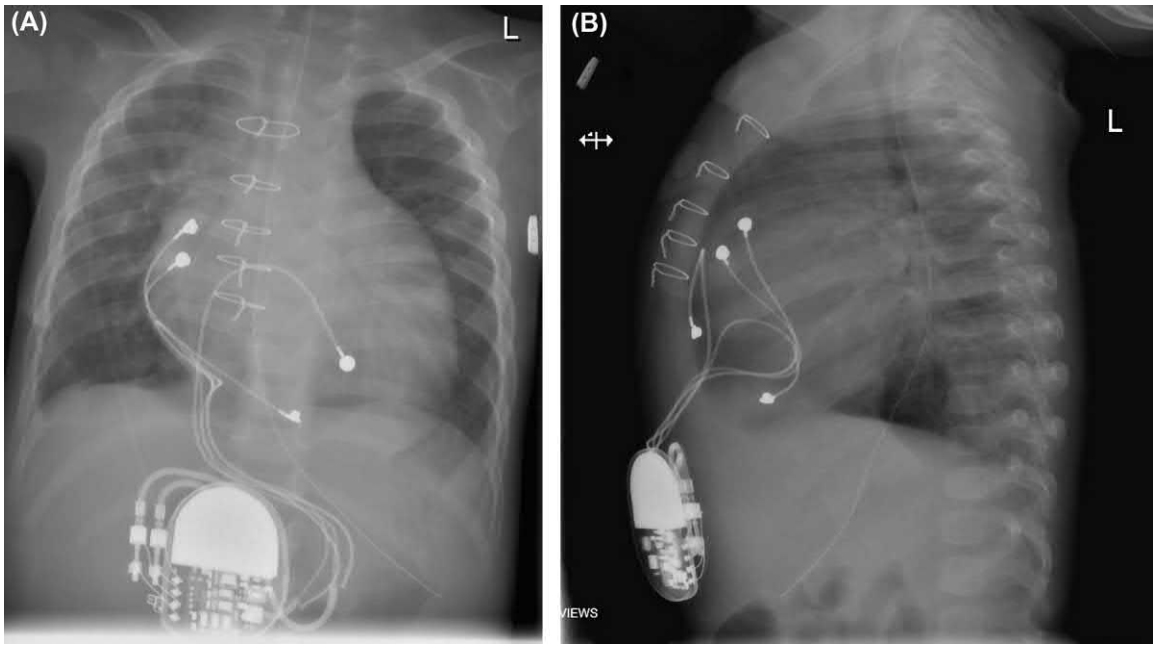

FIGURE 67.10 This chest X-ray is from a 9-month-old female with congenitally corrected transposition of the great arteries (ccTGA). She had complete heart block as well and required a dual chamber epicardial pacing system. Note the epicardial bipolar sew-on pacing leads located on the right atrium and the subpulmonary (morphologically left) ventricle. (A) AP view and (B) lateral view.

nodal reentrant tachycardia [41]. This is similar to the adult population [42].

Any SVT substrate if unrecognized and long lasting can result in a tachycardia-induced cardiomyopathy (TIC). This makes the infant population particularly susceptible. TIC is defined as myocardial dysfunction that is either wholly or partially reversible after control of the responsible tachycardia [43]. Commonly implicated electrophysiologic substrates for TIC include AT, permanent junctional reciprocating tachycardia (PJRT), JT, and ventricular tachycardia. While the substrates described do have a male predominance, TIC itself does not have a sex disposition.

Ectopic AT: Ectopic AT is an automatic tachycardia with incessant AT presenting in over 40% of patients [44] more commonly presenting in male infants. Patients who present at a younger age and with nonincessant AT are more likely to respond to pharmacological therapy. Catheter-based ablation can also be done safely in this population with automatic foci well distributed in both the right and left atria [45] (see Figs. 67.11 and 67.12).

PJRT: This is a persistent macroreentrant tachycardia in which more than 35% of infants will present with symptoms of heart failure and with a TIC [46]. There is a male predominance for this substrate in infants. Medical therapy for PJRT can be difficult with most infants requiring more than a single antiarrhythmic agent [46]. Catheter ablation for PJRT has success rates of >80% with modern mapping techniques [47] (see Fig. 67.13).

Congenital JT: This (JET) is a rather persistent tachycardia presenting within the first 6 months of life (often in the first 4 weeks of life) and presenting with symptoms of cardiomegaly, heart failure, and/or TIC in approximately 60% of infants and a high mortality rate of up to 34% [48]. It is thought to be an automatic, narrow complex tachycardia with atrioventricular dissociation. Interestingly, there may be a familial component to congenital JET in 20% −50% of patients [49,50]. Amiodarone is commonly used for congenital JET, thought 62% of patients required >1 antiarrhythmic agent for rate control [50]; catheter-based ablation, both radiofrequency and cryoablation, can also be used to treat patients with acute success rates of 82% −85% [50] (**see** Figs. 67.14 and 67.15).

Ventricular tachycardias: Ventricular arrhythmias are uncommon in infants. Comorbidities such as cardiomyopathy, primary cardiac tumors, congenital heart disease, or acquired ventricular dysfunction from an in utero ischemic insult or myocarditis should be considered in these patients. Ventricular arrhythmias can also be seen in patients with inherited arrhythmias syndromes, such as LQTS and CPVT. Age distribution for VT is bimodal, occurring in infants and teenagers [51] with responses to therapies being highly dependent on comorbidities (**see** Figs. 67.16 and 67.17).

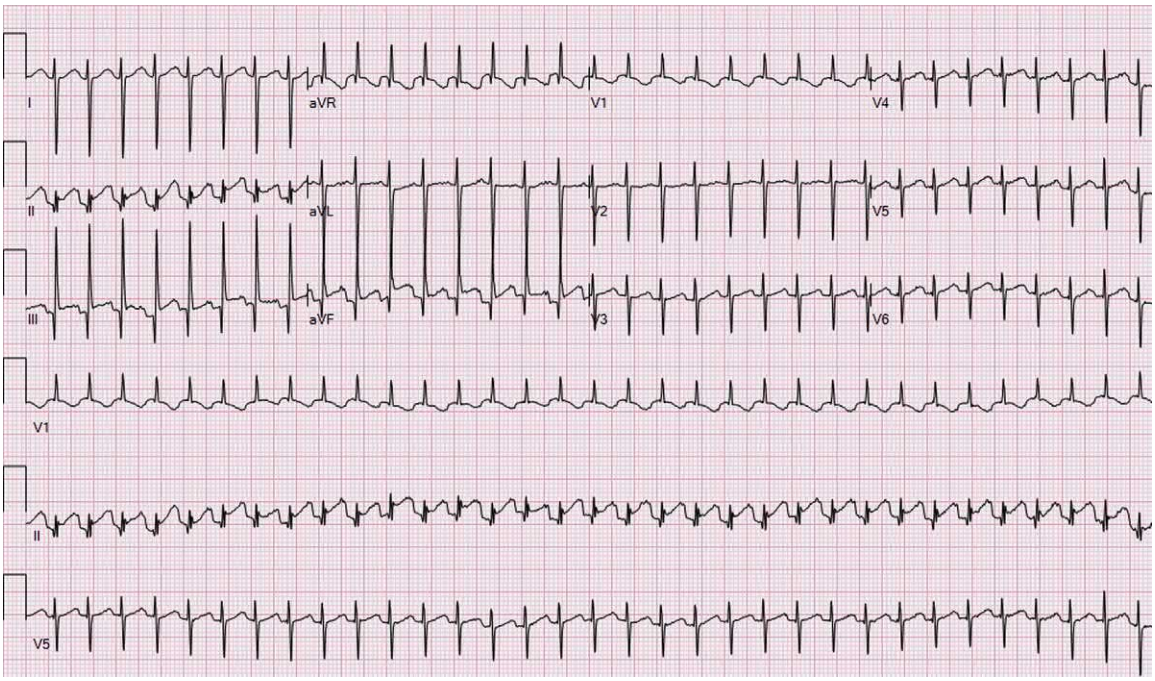

FIGURE 67.11 A 12-lead ECG from a 3-week-old male who presented with heart failure symptoms. This ECG demonstrates an atrial tachycardia at a rate of 200 beats per minute. The P-wave morphology is difficult to clearly discern as the P wave is superimposed on the T wave.

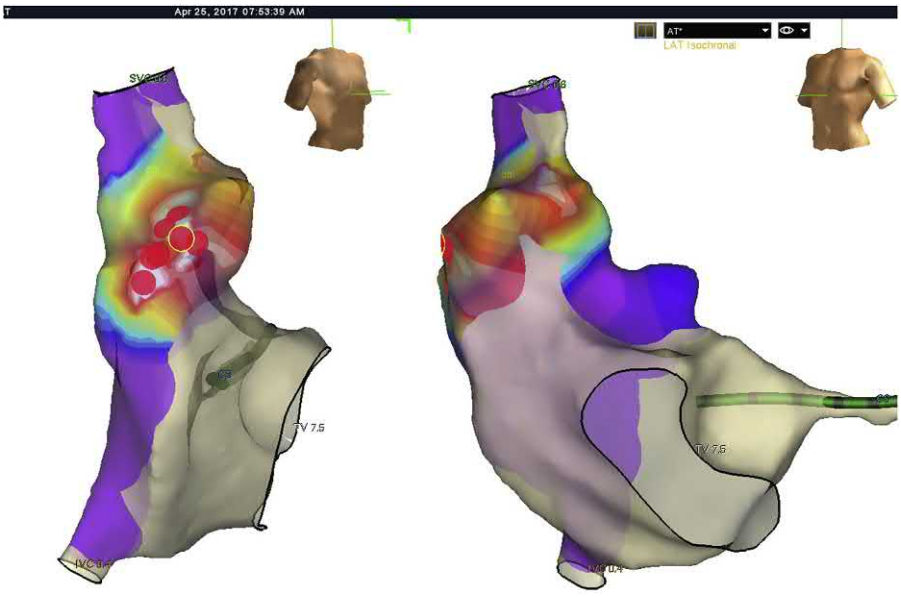

FIGURE 67.12 This is an electroanatomical map (local activation time) from the patient from Fig. 67.11. This 3-week-old patient underwent ablation. The earliest area of activation came from the base of the right atrial appendage. After ablation, the patient had resumption of sinus rhythm.

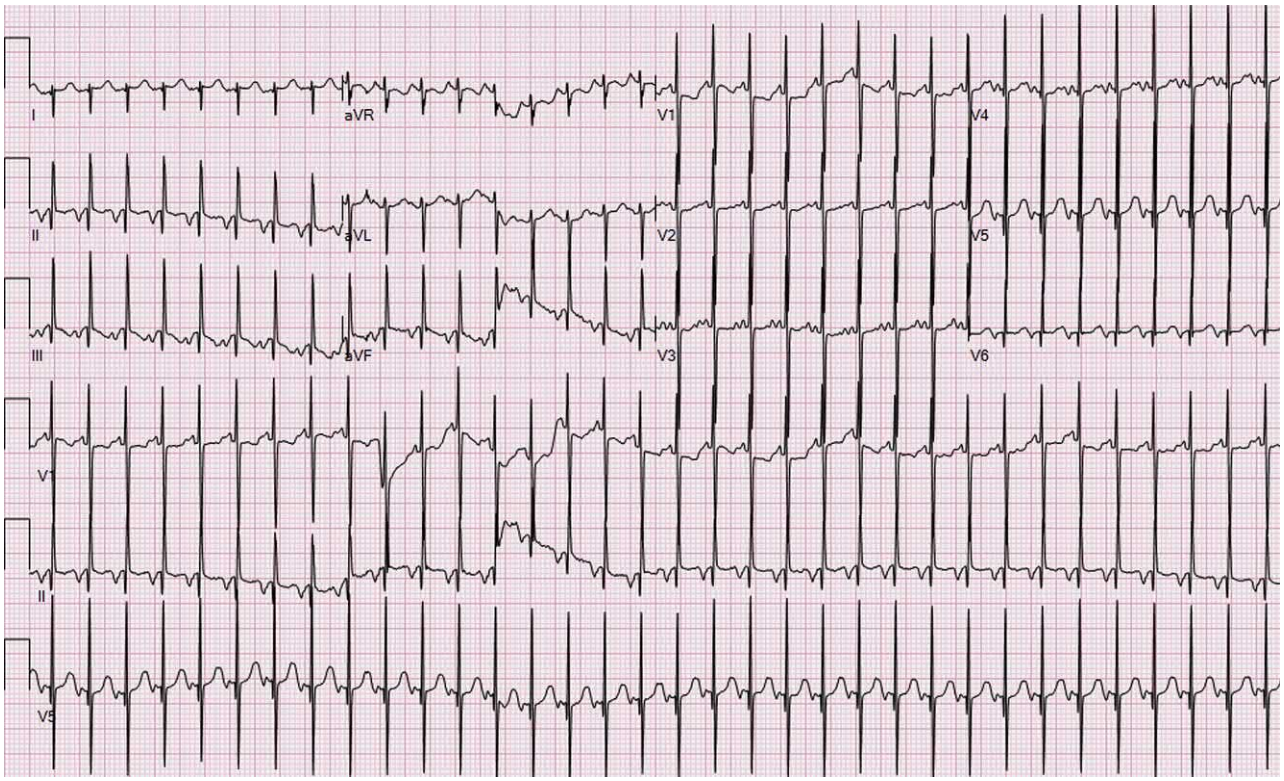

FIGURE 67.13 A 12-lead ECG from a 4-month-old female who presented with heart failure symptoms. The ECG shows a narrow complex tachycardia at a rate of 215 beats per minute and inverted P waves in leads 2, 3, and aVF with a long RP interval, consistent with permanent junctional reciprocating tachycardia.

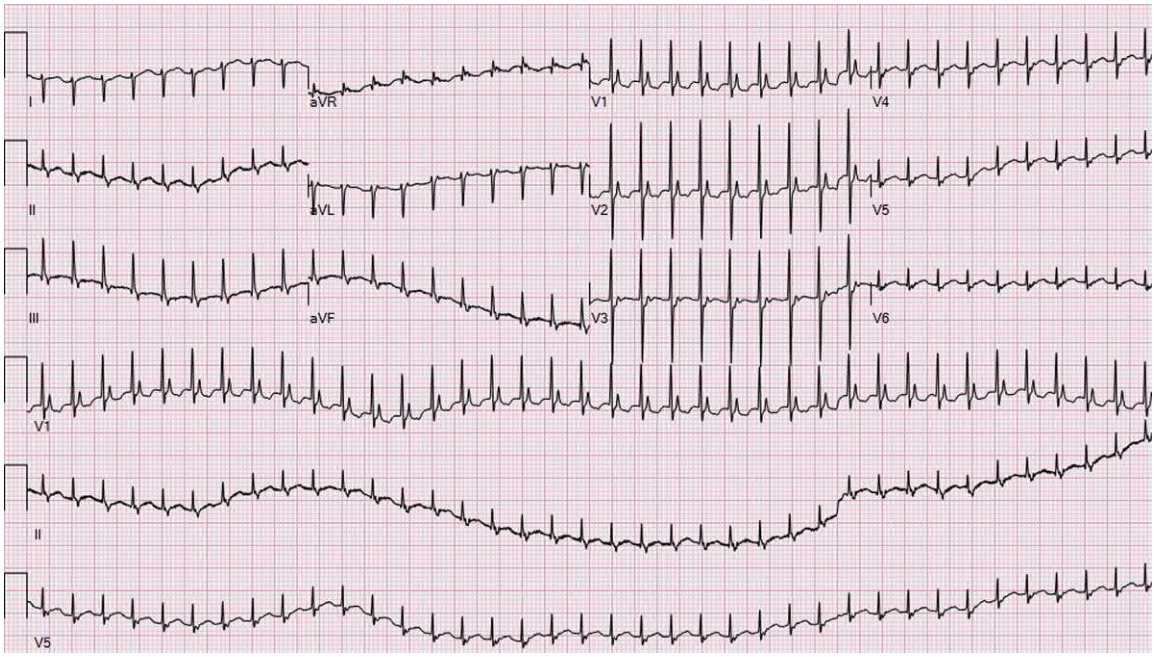

FIGURE 67.14 This is a 12-lead ECG from a 1-week-old male. The ECG demonstrates a narrow complex tachycardia at a rate of 215 beats per minute and atrioventricular dissociation, consistent with junctional tachycardia. Interestingly, this patient had a familial history of junctional tachycardia as well.

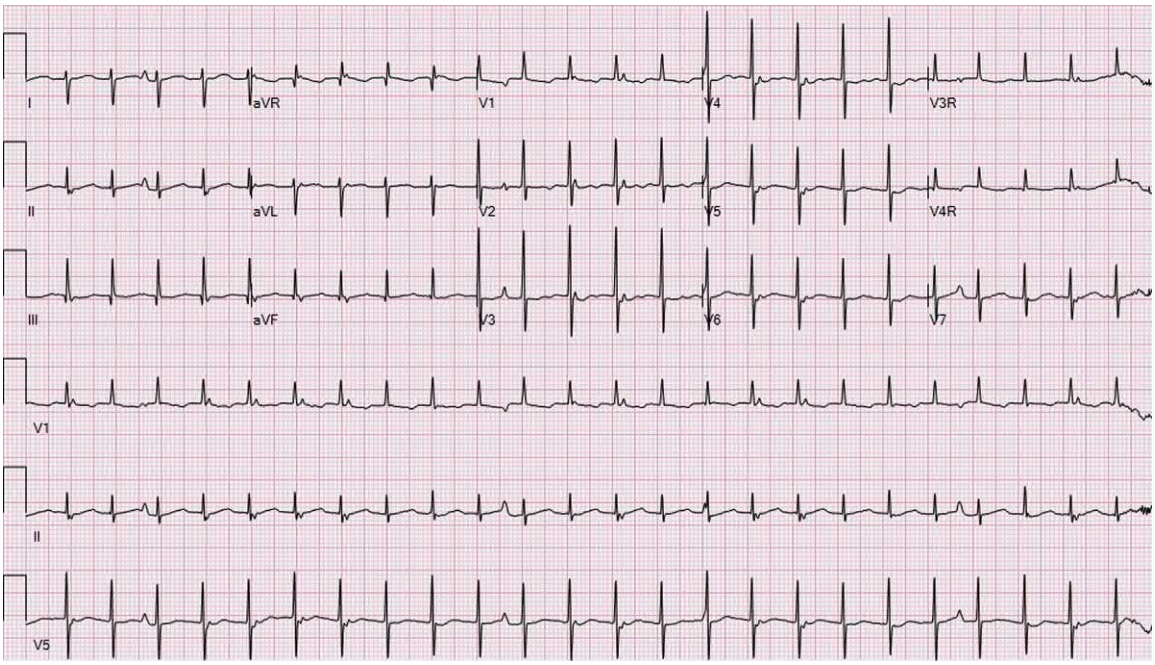

FIGURE 67.15 This is a follow-up of 12-lead ECG from the patient in Fig. 6.14 after starting amiodarone. Now, the rate has slowed to 150 beats per minute though the patient remains in junctional rhythm with intermittently visible P waves.

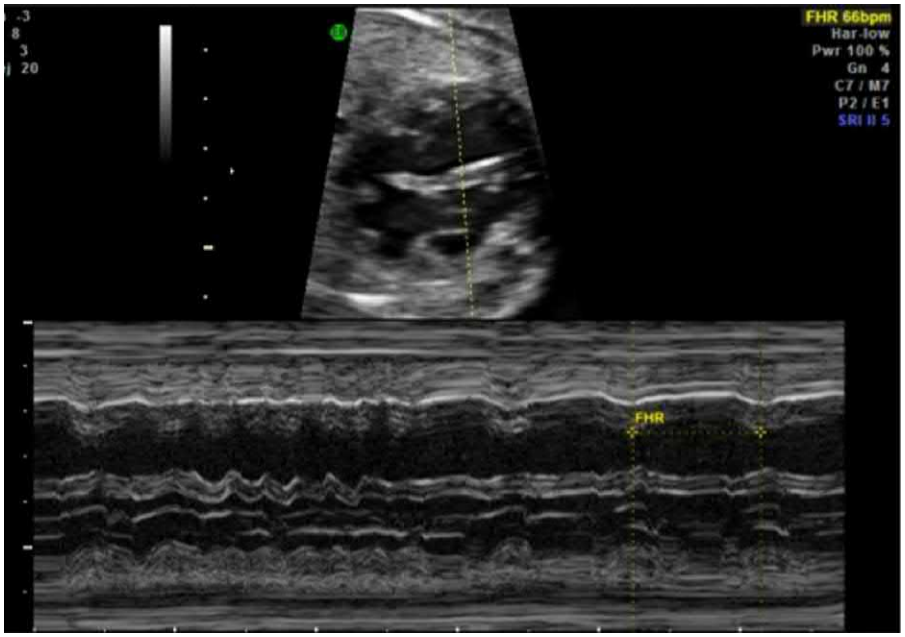

FIGURE 67.16 This is an m-mode from a fetal echocardiogram where the fetus is noted to have intermittent, nonsustained six beat run of ventricular tachycardia, with resumption of presumably sinus rhythm. Note, when the fetus is in a sinus rhythm, the fetal heart rate is quite slow at 66 beats per minute. These findings are concerning for a fetal channelopathy, such as Long-QT Syndrome.

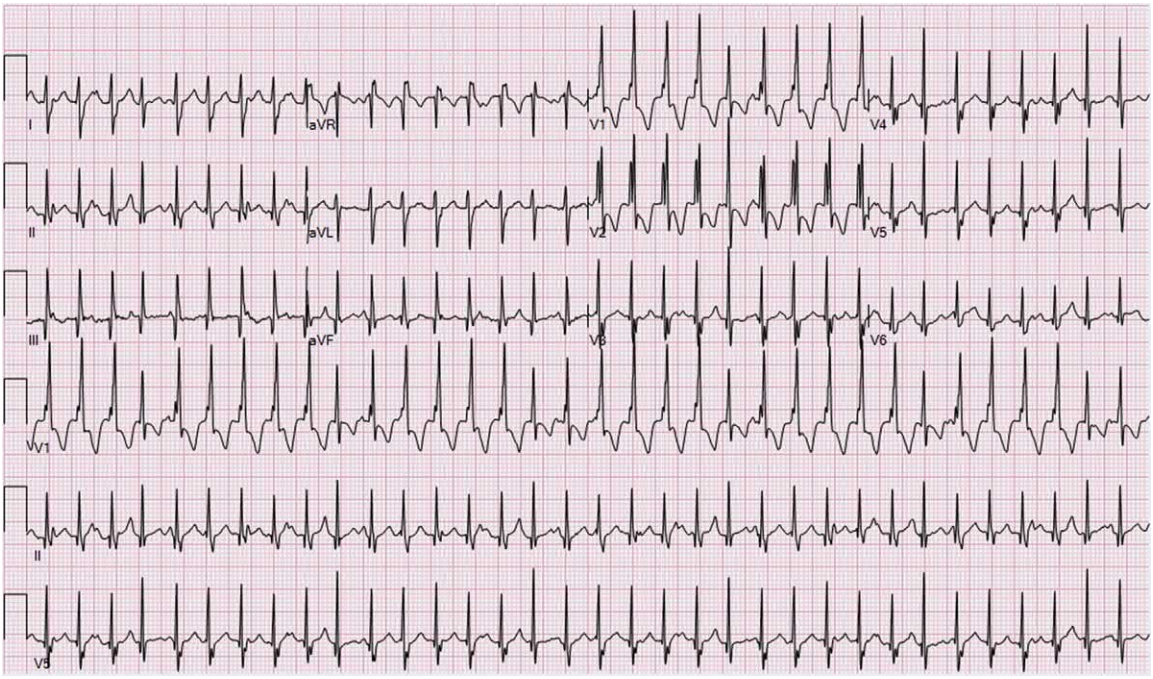

FIGURE 67.17 A 12-lead ECG from a 2-month-old male. The ECG shows a wide QRS for age (88 msec) and a narrow QRS beat interspersed, consistent with ventricular tachycardia with intermittent sinus capture beats.

Summary

There are multiple electrophysiologic substrates implicated in SIDS and other causes of morbidity and mortality in infants with notable sex differences by substrate. Overall, male infants are at higher risk of SIDS, the IASs, and tachycardias that can lead to TIC. As further research continues in this vulnerable population, emerging evidence may help physicians better provide early identification and risk stratification for these infants.

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Chapter 68

Cardiac risk in the young

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Introduction

When facing cardiac risk in the young, the main factor to evaluate and discuss is the risk of sudden cardiac death (SCD). SCD in the young is a critical public health issue. A young life cut short represents a devastating event for families and the society and is associated with many lost productive years. SCD is defined as an abrupt and unexpected death due to a cardiovascular cause, typically occurring within 1 h from the onset of symptoms. There is controversy regarding the age group "young" defines, but it is generally considered as individuals <20 years old. The incidence of SCD in the young vary broadly from 0.6 to 6.2 per 100,000 persons [1−3]. SCD implies the sudden cessation of cardiac activity with hemodynamic collapse, typically due to sustained ventricular tachycardia/ventricular fibrillation.

For the purposes of this chapter, we are going to focus on the three different age group, infants <1 year old, children from 1 to 12 years old, and adolescents from 13 to 19 years old even if this semantic division is in reality a continuum.

Sudden infant death syndrome

Sudden infant death syndrome (SIDS) is the sudden unexpected death of a child younger than 1 year during sleep that cannot be explained after a postmortem evaluation including autopsy, a thorough history, and scene evaluation. The incidence rate is 2 per 100,000 persons [4,5].

Several studies have identified risks associated to SIDS, as shown in Table 68.1 [6,7]. Male sex has been clearly associated with an increased risk for unknown reasons.

Recent data suggests that around 10% of SIDS is associated with an underlying identifiable cause [6]. The main identifiable causes include coronary artery anomalies from the wrong sinus origin, myocarditis, and ion channelopathies. This last encompasses functional cardiac ion channelopathy gene variants, being the most frequent long-QT syndromes (LQTSs) [7]. Other less frequent inherited cardiac conditions need to be considered as well. In particular, Brugada syndrome has been identified as a cause of SIDS in children with severe phenotypic expression [8,9]. Fig. 68.1 shows a 12-lead electrocardiogram of young patients with LQTS Panel A and spontaneous type 1 pattern typical of Brugada syndrome Panel B.

SCD in children ages 1−12

The incidence of SCD in children is widely debated and remains largely unknown, but an expert consensus has estimated it at 0.6 per 100,000 persons [6]. In many countries, there is no mandatory reporting system for juvenile sudden death, making accurate estimation of the magnitude of this problem difficult. A 30-year review has published the aged-related main causes of SCD in the pediatric age in 300 individuals [6]. Table 68.2 summarizes the specific causes in order of frequency. The main cause of SCA in this age group was congenital anomalies (40%).

Pathological ion channelopathy mutations are the cause of 20-30% of electrical SCD in the pediatric age [7]. Long-QT syndrome is the main inherited arrhythmogenic condition, with catecholaminergic polymorphic ventricular tachycardia (CPVT) following behind. Other less frequent causes of SCD in children include coronary artery abnormalities.

Fig. 68.2 shows a detailed account of cause of SCD by age group.

Taking into account external factors, stimulant use for treatment of attention-deficit hyperactivity disorder (ADHD) has been postulated to be a trigger for SCD [10,11].

SCD in adolescents

The incidence of SCD between age 13 and 19 has been calculated at 1.4 per 100,000 persons. In this age group, the majority of arrests occurred in male patients (70%) [6]. The leading cause was presumed primary arrhythmia (23%). The risk of SCD has been calculated to be 1:70,000 persons per year in adolescents.

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TABLE 68.1 Selected Risks Factors and Protective Factors associated with SIDS.

Risk factor	Odds ratio
Birth before 37 weeks' gestation	11.6
Bed sharing <12 weeks of age	10.3
Maternal alcohol use during pregnancy	6.9
Soft bedding	5.1
Birth weight <2500 gr	3.3
Male sex	1.7
Smoke exposure	1.6
Poverty	1.2

A sex difference becomes relevant in adolescence when the hormonal changes allow a malignant expression of certain inherited cardiac conditions in males. On the other hand, women present with longer corrected QT interval, which does not seem to be related to acute effects of estrogens or progesterone or differences in autonomic innervation and is still not completely understood. Young women are also more predisposed than men to Torsades de Pointes. The paradox of a longer corrected QT interval and higher incidence of Torsades de Pointes, but a lower population-based incidence of SCD in women, has not been completely resolved.

When considering the adolescent and young adult, SCD relates to the same diagnoses that have been documented in infancy, with the addition of those triggered by competitive athletics. A study of the incidence of SCD in athletes

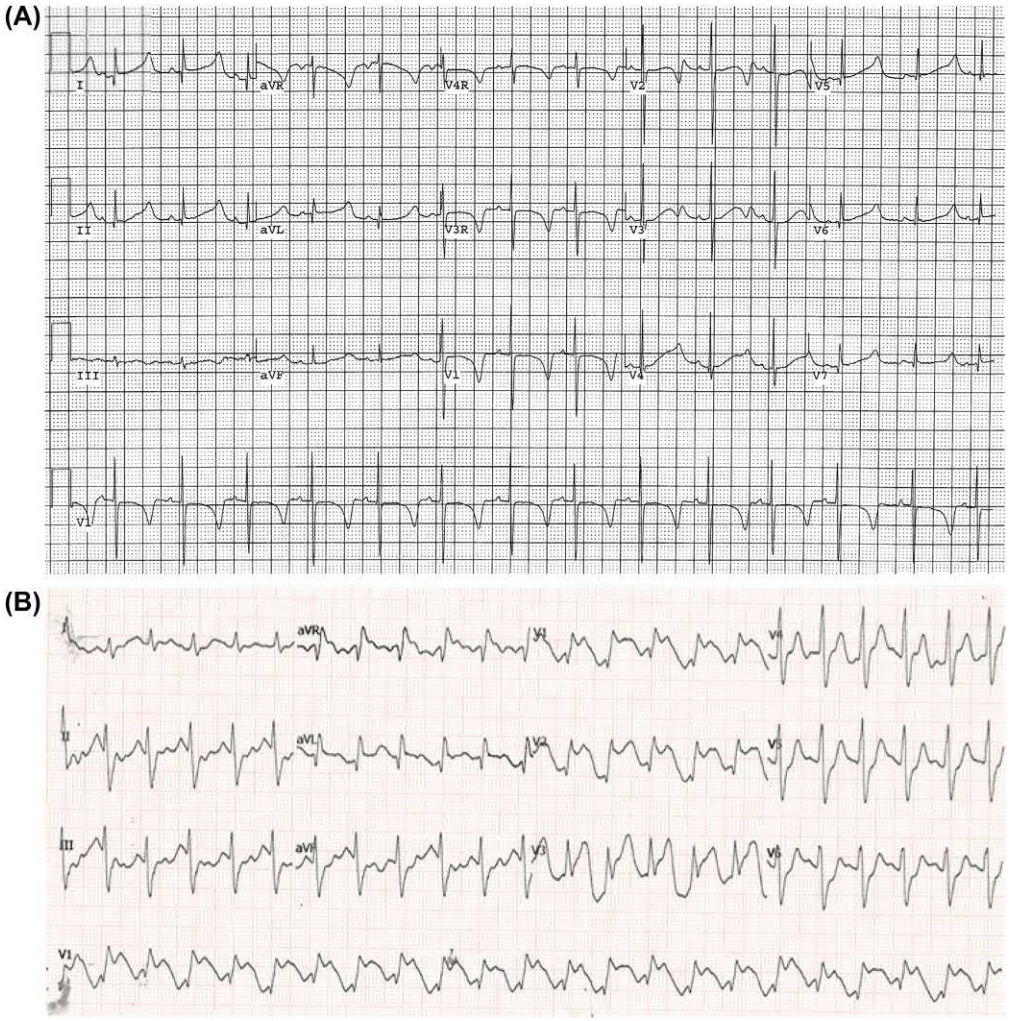

FIGURE 68.1 (A) Panel A shows a 12 lead electrocardiogram of a 6-year-old with LQTS and a corrected QT interval of 540 ms. (B) Panel B shows a 12 lead electrocardiogram with a spontaneous type 1 pattern typical of Brugada syndrome in a 11-month-old presenting with SCD during fever due to a viral infection.

TABLE 68.2 Specific causes of SCD before 20 years of age.

Cause	(%)
Primary anatomical/structural	40
• Structural heart disease[b]	80
• Mitral valve prolapse	10
• Endocarditis	5
• Anomalous origin of coronary arteries	2
• Aortic dissection (Marfan syndrome)	2
• Pericarditis	1
Primary electric	33
• Presumed arrhythmia	65
• LQTS	19
• WPW	7
• Arrhythmia and others[a]	9
Cardiomyopathic	27
• Dilated cardiomyopathy	50
• HCM	23
• Myocarditis	17
• ARVD	8
• LV noncompaction	2

ARVC, arrhythmogenic right ventricular cardiomyopathy; *HCM*, hypertrophic cardiomyopathy; *WPW*; Wolf–Parkinson–White.
[a]*Arrhythmia and others included cases with a history of supraventricular tachycardia, ventricular tachycardia, anomalous atrioventricular, atrioventricular block, catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome, and recurrent ventricular fibrillation of unknown origin.*
[b]*Congenital conditions included tetralogy of Fallot, hypoplastic left heart, atrioventricular septal defects, valvular defects causing insufficiency or obstruction, and transposition of the great vessels.*

demonstrated an overall risk 1:43,000, with higher risk found in male athletes (1:33,000), black male athletes (1:13,000), and male basketball players (1:7000) [12]. In athletic children and adolescents, hypertrophic cardiomyopathy (HCM) plays a predominant role, representing around 30% of cases of SCD [13,14]. In this inherited cardiac condition, the thickened muscle disrupts the heart's electrical system, leading to fast and irregular ventricular arrhythmias. Another rare disease that can be expressed early during sport practice is arrhythmogenic right ventricular dysplasia. Fig. 68.3 shows the difference in causes leading to SCD related and nonrelated to exercise in a population of adolescents and young adults [6].

Questions exist about the relative risk of SCD in competitive athletes versus the general population and whether this risk requests a separate, more advanced cardiovascular screening program in athletes. It is generally accepted that exercise and intense physical exertion through athletic participation increase the likelihood of sudden death for many disorders predisposing to SCD.

Although it is widely held that athletic activity results in a higher risk of SCD, there is significant controversy concerning whether stimulants for ADHD, other medications, or dietary supplements may contribute to increase the risk in this population.

One of the main difficulties in attempting a retrospective diagnosis following an event of SCD in the young lies in the fact that the results do not reveal a cause in most of the cases. Autopsy-negative deaths may be due to inherited arrhythmia syndromes and ion channel disorders such as LQTS, short-QT syndrome, Brugada syndrome, and CPVT or other primary electric diseases such as Wolff–Parkinson. In this last scenario, the presence of preexcitation, an abnormal anterograde electrical connection between the atria and the ventricle that is able to conduct electricity at high rates, puts children and adolescents at risks particularly during exercise-induced atrial fibrillation rapidly conducted to the ventricles via the abnormal AV connection. This can culminate in SCD associated with sports practice and cannot be identified unless there is evidence of a 12-lead electrocardiogram with WPW previous to the event (Fig. 68.4).

The accurate diagnosis of ion channelopathies postmortem is still limited; however, postmortem genetic testing (so-called molecular autopsy), is able to identify a pathogenic cardiac ion channel mutation in more than one-third of unexplained SCD cases [15–17].

Risk assessment and SCD prevention in the young

There is significant discordance among experts in the field about the best approach to prevent SCD in children and young people. Some experts support the implementation of large-scale cardiovascular screening programs in all children to identify at-risk individuals in an effort to prevent SCD. A basic cardiovascular screening strategy involves the addition of an electrocardiogram to the sport screening. A deeper screening modality includes echocardiography and exercise test. Data from the Veneto region of Italy suggest that ECG screening can successfully identify at-risk cardiovascular diseases and dramatically reduce the incidence of SCD in competitive athletes [18,19]. Critics of ECG screening claim lack of clinical accuracy adds unnecessary costs clinical, as well as financial, and emotional consequences in cases of false-positive screening test results [20].

A moderate position advocates for screening in selected age groups and target population, including infants, athletes, patients with ADHD, and patients who have a family history of SCD. Previous screening studies have generally

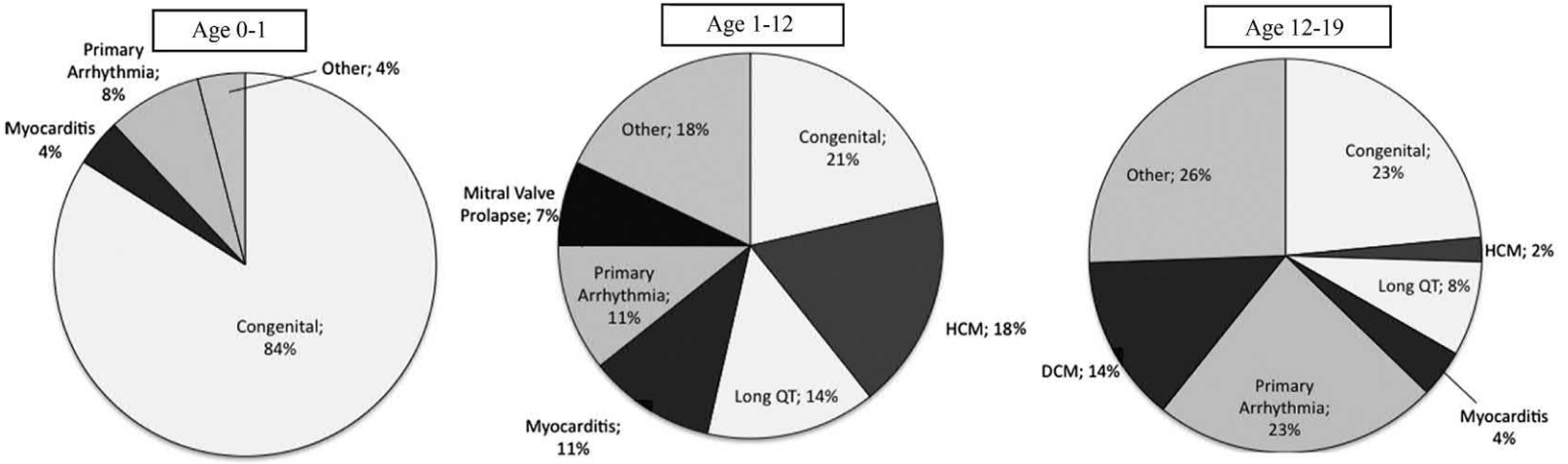

FIGURE 68.2 Detailed causes of SCD by age group. *CAD*, coronary artery disease; *DCM*, dilated cardiomyopathy; *HCM*, hypertrophic cardiomyopathy. Other corresponds to all other causes.

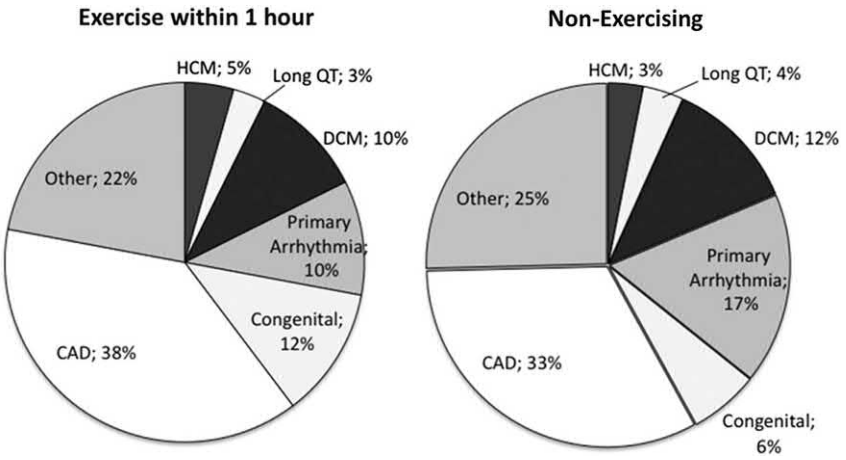

FIGURE 68.3 Exercise- and non−exercise-related causes of SCD in young individuals. *CAD*, coronary artery disease; *DCM*, dilated cardiomyopathy; *HCM*, hypertrophic cardiomyopathy. Other corresponds to all other possible causes.

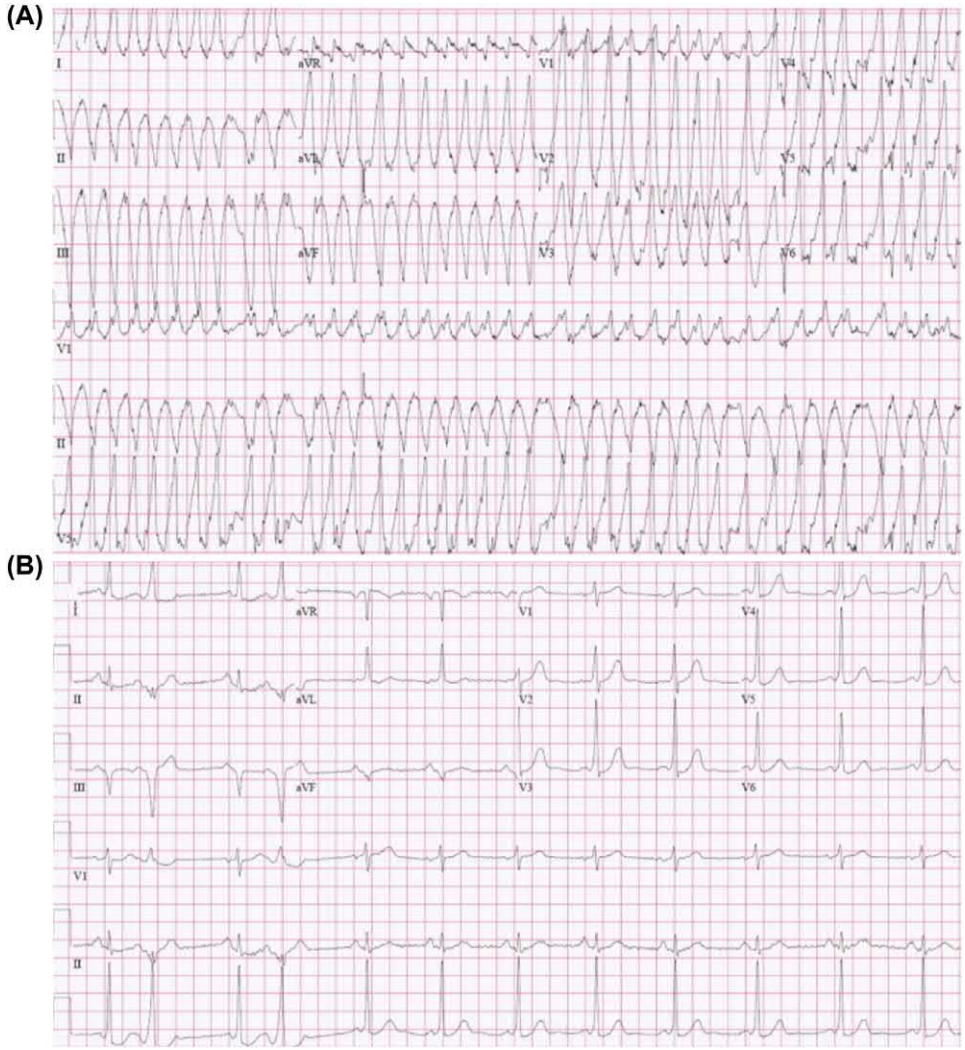

FIGURE 68.4 12-Lead Electrocardiograms of preexcited atrial fibrillation during exercise due to WPW. Fig. 68.4. (A) 12-lead electrocardiogram of a 13-year-old patient presenting with SCD during exercise, with evidence of a rapidly conducted atrial fibrillation. (B) 12-lead electrocardiogram of the same patient after direct current cardioversion, showing sinus rhythm with a delta wave.

included small patient populations [21,22]. A notable exception to this is the work by Schwartz et al. [23,24] who evaluated ECG screening in large populations of neonates in Italy.

When considering young population screening, there seems to be consensus to address age-specific issues relative to the characteristics of the test and the diseases of interest. For instance, a screening study in infants needs to focus on the measurement of the QT interval, whereas ECG in older children and adolescents would focus on markers of HCM and WPW. Moreover, in children 0−12 years of age, congenital anomalies were the most common cause of SCD, suggesting that enhanced postnatal diagnosis and management of congenital cardiac disorders may provide the largest impact on the prevention during childhood.

With the rapid development in the field of pediatric SCD both in terms of diagnosis and acute treatment, the next years will probably see a detailed characterization of the causes affecting different sex and age groups. This knowledge should give evidence to help to the development of targeted screening programs and more effective strategies for prevention of these catastrophic events.

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Chapter 69

Sex-specific mechanisms of sudden cardiac death

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Sudden cardiac death (SCD) results in an estimated 180,000 to >450,000 deaths in the United States annually [1]. The ACC/AHA/ESC 2006 guidelines define SCD as "death from an unexpected circulatory arrest, usually due to a cardiac arrhythmia occurring within an hour of the onset of symptoms" [2]. Sudden death is estimated to be the most common cause of death in the country [1].

Women have an overall lower risk of SCD than men—even after adjusting for predisposing risk factors such as coronary artery disease (CAD), myocardial infarction (MI), and heart failure (HF) [3]. Among the general population, the public health burden of SCD in the United States study found that the incidence of SCD was 45 per 100,000 in women and 76 per 100,000 in men [4]. Data from Framingham reveal that for individuals without pre-existing cardiovascular disease, women have a 4-fold increased risk of SCD post-MI, whereas men have an 11-fold increased risk [3,5,6], while for those with a diagnosis of CAD, long-term risk of SCD increases by 3.3-fold in men and 1.9-fold in women. HF increased risk of SCD by 4.8-fold in men as opposed to only 1.5-fold in women in the Framingham study [7]. Similarly, a pooled analysis was performed of five clinical trials and registries of ambulatory HF patients without devices but who meet guideline indications for ICD or CRT therapy. Using the Seattle Heart Failure Model to predict annual mortality, women were found to have a 32% lower risk of SCD than men [8].

However, while less common than in men, roughly 150,000 cases of SCD in the United States occur in women annually, representing the fifth leading cause of death after overall heart disease, all types of cancers combined, cerebrovascular disease, and chronic lower respiratory disease [4]. A study by Stecker et al. analyzed the public health burden of SCD in the United States. Using data from the Oregon Sudden Unexpected Death Study (SUDS), US death certificate reporting, and population data from the US Census Bureau, the study assessed the years of potential life lost (YPLL) to SCD as compared with other causes of premature death. In women, SCD is the third leading cause of premature death after all cardiac causes combined and all cancers combined. Premature deaths caused by SCD exceed death from any individual cancer in women. It is responsible for 41% of YPLL lost to cardiovascular disease [4].

The majority of SCD in both men and women results from ventricular tachyarrhythmias. Two-thirds of SCD cases are due to ventricular tachycardia (VT) that can rapidly degenerate to ventricular fibrillation (VF), while a third of SCD cases result from bradyarrhythmias or asystole [9]. The presenting rhythm in the majority of women with cardiac arrests is VT or VF [5]. The Oregon SUDS study showed a higher incidence of pulseless electrical activity (PEA) (31.5%) or asystole (30.5%) in women than in men (24.5% and 20.7%, respectively) presenting with SCD [10]. However, VT and VF can rapidly degenerate to asystole or PEA. It is possible that difference in presenting rhythm at time of arrest partially stems from differences in time to arrival of emergency medical services rather than differences in pathophysiology. An autopsy series of 534 patients with sex and control comparison showed that women are more likely to have SCD at home than men [11], which is also found in an analysis of the Nurses' Health Study Cohort [5]. Similarly, a metaanalysis of 409,323 patients showed that women are less likely to have a witnessed cardiac arrest and were less likely to present with an initial shockable rhythm. This suggests that the initial rhythm during SCD may begin as VT/VF in both men and women, but in women, the rhythm may have degenerated during the time to response of emergency personnel to unwitnessed out-of-hospital arrests [4]. Higher survival rates are seen in women presenting with SCD with a shockable rhythm—likely related to time to medical response—highlighting the

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impact of the delay in receiving medical attention on survival rates for women after SCD [5,12].

Epidemiologic differences in SCD in women as compared with men suggests that differences in arrhythmogenic substrate, hormonal effects, and susceptibility to triggers may all play a role. In general, the underlying etiology of SCD may be related to primary cardiac arrhythmias or arrhythmias arising from needs space between from and CADCAD, cardiomyopathy, or hypertensive heart disease [13]. Overall, the most prevalent cause of SCD in both men and women is ischemic heart disease [14], although the percent attributable to ischemic heart disease is lower in women, 34% in one study and 71.7% in another, than men, 46% in one study and 75.7% in the other [6,14]. Two autopsy series found CAD was more frequently the cause of SCD in men than in women [11]. This is likely due to the protective effects of estrogen against coronary disease, which results in a lag time in development of CAD in women compared with men [15]. Cardiomyopathy frequently results in SCD, and women were more likely to have a nonischemic cardiomyopathy as a cause of SCD than men [14].

Among survivors of SCD, women also have ECG abnormalities more frequently than men. The Fingesture study found repolarization abnormalities on ECG was more common among women with SCD than men [14]. Therefore, women may be more susceptible to ventricular arrhythmias related to repolarization. A retrospective study also found that women are more likely to present with SCD in the absence of structural heart disease, making it more difficult to predict and prevent SCD in women [7]. This highlights the importance of understanding the mechanism, risk factors, and triggers of SCD in women.

Coronary disease

CAD is the most common underlying pathology resulting in SCD and is related to 70%–80% of SCD cases [11,14,16,17]. Cardiac ischemia and reperfusion abnormalities result in electrophysiologic changes with heterogeneous local conduction velocity and repolarization, as well as alterations in anisotropy. This results in an increased risk of ventricular arrhythmias and SCD. The most common mechanisms for SCD in patients with CAD are polymorphic VT and monomorphic VT degenerating into VF [18]. Among patients with a prior myocardial infarction, women are 2.5 times less likely to have SCD than men [5,19]. This is likely due to electrophysiologic substrate, hormonal, and autonomic differences in women and men. However, the overall survival rate is similar between men and women presenting with SCD in the setting of CAD [20,21].

Even among patients with SCD related to CAD, there are sex-related differences that suggest differences in arrhythmogenic substrate and susceptibility to triggers. Women present with SCD at an older age than men, and the risk of SCD doubles with each decade of life [15,19,22]. The incidence of SCD mirrors the pattern of gradual increase CAD in women at an older age than in men. In women, the incidence of heart disease and SCD rises slowly over the course of their lives, unlike men whose risk begins to increase at 35–45 years of age [4]. This is believed to be due, at least in part, to hormonal differences affecting the development of CAD. Men also typically present with more extensive CAD and a greater burden of myocardial scar. However, in a population of patients with CAD, women were observed to be less prone to ventricular arrhythmias than men, even after controlling for differences in substrate, suggesting a more complex interplay between substrate and susceptibility to triggers of ventricular arrhythmias [23].

CAD also presents itself differently in women than in men. The CASS trial showed women have less obstructive CAD on angiography than men, although only a small percent of the study cohort were women [24]. Although mortality increases in correlation with CAD severity, the incidence of SCD does not correlate with the severity of coronary stenosis seen on angiogram. This raises the question of whether microvascular disease is a contributor to electrophysiologic changes in the ventricular myocardium in women. The WISE study showed women are more likely to have microvascular disease and ischemia as identified by cardiac magnetic resonance imaging, whereas men typically have intraluminal plaque in the epicardial arteries. Women may also have plaque erosion and stenosis that is more difficult to diagnose by angiography [25]. The limitations in diagnosing CAD in women pose challenges to identifying significant CAD as a risk factor for SCD in women. It may also lead to women receiving less aggressive therapies, which may be why there is no sex difference in event-free survival or all-cause mortality despite the lower incidence of sustained ventricular arrhythmias [20,22,26,27]. It is, therefore, critical to recognize and aggressively treat cardiovascular risk factors in women.

Overall, risk factors for cardiovascular disease seem to be as strongly associated with SCD in women as in men [19], although specific factors play different roles in men and women. For example, diabetes increases mortality risk in women more than in men, eliminating the protective effects of female sex [19]. Lipoprotein cholesterol levels result in higher risk of CAD in women than men. There is a direct correlation between the incidence of SCD in women and traditional cardiovascular risk factors of age, diabetes mellitus, and smoking [19,28]. Additionally, a prospective

study of 72,484 women found that higher body mass index, another risk factor for CAD, was associated with greater risk of SCD [29]. Particularly in light of the difficulty in diagnosing CAD in women as mentioned previously, aggressively modifying risk factors for CAD is critical in lowering the risk of SCD as well as cardiovascular mortality in women.

Interestingly, women with known CAD and implantable cardioverter defibrillators (ICDs) also had fewer episodes of VT/VF than men [30] (Fig. 69.1), even after controlling for multiple risk factors such as ejection fraction. This suggests differences in electrophysiologic substrates, hormonal or autonomic milieu, or response to triggers that affect susceptibility to lethal ventricular arrhythmias and thus likely contribute to the sex difference in incidence of SCD.

Electrophysiologic substrate and hormonal effects

In both those with known heart disease and those without risk factors for SCD, there are known sex-based differences in cardiac physiology that likely contribute to the differences in malignant arrhythmias, leading to sudden cardiac death. Men and women have different cardiac electrophysiologic properties, some due to differences in substrate from the impact of sex hormones during cell development, and others from the effects of circulating sex hormones. As described in detail elsewhere, estrogen, progesterone, and testosterone affect the protein synthesis of select ion channels as well as ion channel function by mediating signal transduction pathways. Some of these differences may be protective, whereas others are proarrhythmic, thus promoting different mechanisms of SCD in men versus women.

There are sex-based differences in excitation–contraction coupling in cardiomyocytes that may decrease the risk of malignant arrhythmias in women as compared with men [31]. At faster pacing rates, female rat ventricular myocytes exhibited smaller and slower contractions compared with male cardiomyocytes [31]. This correlated with smaller calcium transient amplitudes from sarcoplasmic reticulum calcium release into female cardiomyocytes [31]. The gain of excitation–contraction coupling in female cardiomyocytes was also half that in males under physiologic membrane potentials. This led to a slower rate of calcium flux intracellularly, with reduced release of calcium from the sarcoplasmic reticulum during physiologic stress [31]. This intrinsic protective mechanism appears to prevent calcium overload at faster heart rates, lowering the risk of ventricular arrhythmias in females. Cardiomyocytes from women with HF also demonstrated less calcium leak from the sarcoplasmic reticulum compared with cardiomyocytes from men [32]. Intracellular calcium overload leads to delayed afterdepolarizations and ventricular arrhythmias in HF, and this may explain why lower rates of ventricular arrhythmias are seen in women with HF as compared with men [32].

However, other hormonal effects may be proarrhythmic in women. Women have reduced expression and function of potassium channels in their ventricular myocardium compared with men [33]. Estrogen decreases the flow of rapid delayed rectifier potassium currents (I_{kr}) in the ventricular myocardium [34]. This results in longer ventricular action potential duration, longer ventricular refractory periods, and longer QT intervals. As sex hormone levels change during development, the QT interval correspondingly shortens in men after puberty, whereas women have longer physiologic corrected QT intervals.

Longer QT intervals result in a higher predisposition to ventricular arrhythmias. Analysis of data on 904 women from the Women's Ischemia Syndrome Evaluation (WISE) study identified a longer corrected QT interval to be only independent risk factor for SCD in women without obstructive CAD [28].

The proarrhythmic implications of the differences in repolarization are most clearly exemplified in the channelopathies. In long QT syndrome 1 (LQT1), mutations in the KCNQ1 gene result in defective IK_s potassium channels. Boys have a higher incidence of ventricular arrhythmias and SCD than girls until puberty, when the risk of SCD reverses between sexes [35]. In long QT syndrome 2 (LQT2), mutations in the KCNH2 gene result in abnormal IKr potassium channels. Females of all ages carry a higher risk of cardiac events and SCD than their male counterparts [35–37]. The risk of arrhythmic events and SCD further increases for these women with LQT2 in the peripartum period—particularly in the postpartum period 9–12 months after delivery [38].

In addition to affecting action potential duration, sex hormones also increase the expression and function of calcium current [34]. Estrogen increases the flow of L-type calcium current by affecting ryanodine receptors, which increases sodium–calcium exchange and may predispose women to early afterdepolarizations and triggered activity, increasing the risk of ventricular arrhythmias [34,39,40].

Based on the electrophysiologic differences, women also more prone to developing drug-induced prolonged QT and torsades de pointes (TdP) than men after administration of drugs that prolong cardiac repolarization. Two-thirds of drug-induced TdP occur in women [41]. This was seen with I_{kr} blocking medications and QT-prolonging agents, including antibiotics such as erythromycin, antipsychotics such as chlorpromazine, the antimalarial drug halofantrine [40–43]. There is also extensive evidence that women have a higher risk of TdP and SCD from antiarrhythmic drug

therapy [39,44–50]. The DIAMOND study population of post-MI cardiomyopathy patients demonstrated a 47% risk of TdP in women compared with 28% in men with dofetilide use [49]. Other studies found sotalol had a greater QT-prolonging effect in women than in men, and women had a 4.1% risk of TdP with sotalol therapy compared with a 1.9% risk of TdP in men [46,51]. Similar trends in the risk of TdP were seen with quinidine and ibutilide therapy, with higher rates of TdP in women as compared with men [45,48]. Particular care should, therefore, be taken to carefully monitor the QT interval, potassium level, and volume status in women on QT-prolonging agents—particularly during initiation of class IA and III antiarrhythmic medications.

Circulating hormones also play a role in the sex-based differences in the risk of SCD. Women's QT intervals also fluctuate in duration based on variations in estrogen and progesterone levels, with QT intervals varying during the ovarian cycle when there are large fluctuations in estrogen and progesterone levels [52,53]. This correlates with the observed increase in incidence of arrhythmias, including TdP, in women during the menstrual phase when estrogen levels are high [53,54].

Progesterone and testosterone both increase slow delayed rectifier (I_{ks}) potassium currents and decrease L-type calcium currents, which shortens the ventricular action potential duration [55–57]. Accordingly, progesterone appears to have a protective effect from arrhythmias and SCD, whereas estrogen appears to be arrhythmogenic based on a rabbit model of long QT syndrome (LQTS) [58]. This was also seen in healthy women with drug-induced (acquired) LQTS [54]. Women had a greater risk of a drug-induced arrhythmia during menstruation and during the follicular phase when estrogen levels are high, as compared with the luteal phase when progesterone levels are high.

Sex hormones also appear to affect penetrance and disease severity for certain cardiomyopathies, including arrhythmogenic right ventricular cardiomyopathy (ARVC). Penetrance in ARVC is three times higher in men than in women, and men are typically more severely affected with a higher risk of ventricular arrhythmias [59]. However, this effect does not apply to all cardiomyopathies, and the mechanism is not well understood.

Effects of autonomic activity

Autonomic activity regulates susceptibility to cardiac arrhythmias and is an important factor in the creation of an arrhythmogenic milieu. Men and women have known differences in autonomic nervous system function. From puberty until menopause, women have consistently higher baseline heart rates than men, implying an influence of sex hormones on autonomic tone [60,61]. Heart rate variability (HRV), or the beat-to-beat variation of heart rate over time, reflects the balance of sympathetic versus parasympathetic regulation of the sinus node [62]. Women have higher heart rate variability than men, suggesting that women have a higher baseline vagal tone than men. However, baroreflex sensitivity—another indicator of antiarrhythmic autonomic regulation—is lower in middle-aged women than men [62]. There are manifest differences in the effects of autonomic activity on the electrophysiological properties of the heart between men and women. In the baseline state, men have longer sinus cycle length and sinus node recovery time than women and also have longer AH intervals, AV nodal effective refractory period (ERP), and Wenckebach cycle length (WCL) than women, as well as lower ventricular ERP and shorter QTc than women [63–66]. However, autonomic blockade eliminated the differences in sinus node properties between men and women, as well as the shorter AV node refractoriness and conduction time, shorter QT and JT duration, and lower right ventricular refractory period in men, implying that these differences are due to differences in autonomic tone rather than cellular electrophysiology [62]. These differences in ventricular myocardial conduction properties may contribute to higher arrhythmogenic susceptibility for ventricular arrhythmias and SCD in men.

Autonomic reactivity to triggers and arrhythmogenesis

In addition to differences in resting autonomic tone, there are also differences in autonomic reactivity to stress between men and women. Psychologic stressors cause fluctuations in autonomic tone, which appear to be arrhythmogenic, and have been strongly implicated in arrhythmias and SCD [67–70]. Natural disasters are associated with an increased incidence of SCD, and anger-induced T-wave alternans were seen to predict future ventricular arrhythmias in patients with ICDs [71–74]. In women with LQT2, sleep deprivation was associated with arrhythmic events and SCD [75].

Acute psychologic stressors may be less potent in triggering of malignant ventricular arrhythmias and SCD in women than in men. Women have a lower adrenergic response to mental stress than men [76]. Accordingly, SCD in men was more often preceded by a stressful event [77]. Similarly, shifts in sympathetic tone in response to provocation appear to be lower in women. These differences in autonomic response to stressors may account in part for the differences in susceptibility to SCD between men and women with similar substrate, risk factors, or triggers. Similarly, women also seem less likely to have exertion-related SCD [23,77–81]. As noted earlier, a study in patients with CAD and ICDs confirmed that men were more likely to have ventricular arrhythmias compared with women [30] (Fig. 69.1). This suggests that among patients

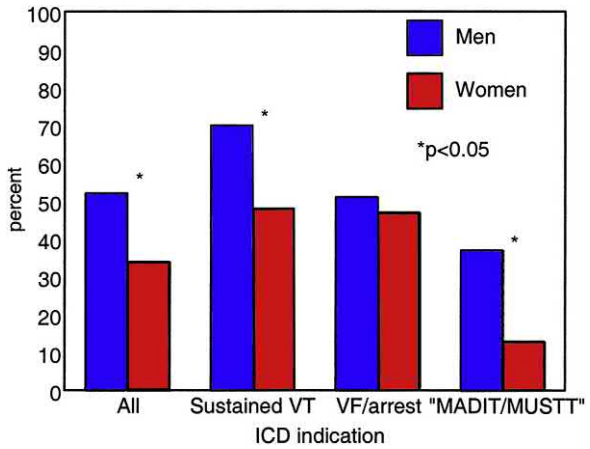

FIGURE 69.1 Incidence of any ventricular tachycardia (VT)/ventricular fibrillation (VF) after implantable cardioverter defibrillator (ICD) implantation in men versus women, for the entire population and by indication for ICDr. *MADIT*, Multicenter Automatic Defibrillator Implantation Trial; *MUSTT*, Multicenter UnSustained Tachycardia Trial. *Modified with permission from Lampert et al, [30].*

with similar substrates of ischemia-induced scar after MI, there is a sex-based susceptibility to SCD that may in part be due to triggers that initiate arrhythmia.

Furthermore, women with acute coronary events have more vagal activation than men, which may have antiarrhythmic effects [62,82]. This may explain why women experience fewer ventricular tachyarrhythmias than men during cardiac ischemia, as the likelihood of VF increases during ischemia due to an increase in sympathetic tone and increasing vagal tone is protective [83–87].

In addition to acute stress, chronic stressors also play a role in SCD, with a strong associations demonstrated between depression—a chronic psychologic stressor, use of antidepressants, and SCD in both men and women. Multiple studies have found that depression is an independent risk factor for ventricular arrhythmias and SCD in women. A prospective study of 645 patients with ICDs found that the severity of symptoms of depression was a predictor for shocks for VT or VF [88]. The Nurses' Health Study and the Women's Health Initiative both found that symptoms of depression put women at higher risk for fatal CAD events [89,90]. Mehta et al. found that in their overall cohort of women, a history of depression independently predicted risk of SCD [28]. This may be related to the more potent QT-prolonging effects of some antidepressants such as SSRIs in women and is an area for further study. However, the study also found that more women were depressed than men, raising concern that this risk factor for SCD may be more prevalent in women than in men.

Conversely, modulating autonomic tone—particularly increasing vagal tone—through increased exercise lowered the risk of SCD in women. Data from the Heart and Estrogen/Progestin Study demonstrated that women who exercise at least three times a week had decreased SCD [91,92].

Summary

While women have a lower risk of SCD than men, SCD is one of the leading causes of premature death in women. There are known differences in hormonal, autonomic, and electrophysiologic properties between men and women, leading to distinct sex-specific mechanisms of SCD. Some differences confer a protective effect against ventricular arrhythmias in women, whereas others are proarrhythmic. These differences are implicated across a range of pathologic states, including coronary disease and myocardial infarction, cardiomyopathies, and channelopathies. The most common mechanism for SCD is ventricular arrhythmias—particularly due to ischemia or myocardial scar-based reentry from CAD. Estrogen impacts calcium handling and excitation–contraction coupling and decreases ventricular arrhythmias in women. However, estrogen also affects intracellular potassium currents, resulting in abnormal repolarization with an increase in QT interval and an increased risk of TdP in the LQTS and in acquired LQT due to QT-prolonging drugs.

There is growing but still limited understanding of how the sex-based differences clinically impact risk assessment and management of women at risk for SCD. Greater understanding of the sex-specific mechanisms of SCD would improve risk assessment, improve care, and improve allocation of resources in preventing SCD in women. A greater representation of women in studies of SCD and ventricular arrhythmias, as well as further sex-specific studies on women with SCD, would add to the current understanding and help improve outcomes in women with SCD.

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Chapter 70

Sex-specific risk assessment of sudden cardiac death

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Introduction

Sudden cardiac death (SCD) is commonly defined as death that occurs within 1 h of the onset of acute symptoms. Despite advancements in treatment of SCD, survival remains abysmal [1], and there are substantial challenges in the identification of individuals at highest risk. This problem stems from the wide variety of underlying mechanisms and pathologies that can lead to SCD, the lack of both sensitive and specific predictive markers, and absence of a mechanism to effectively screen the general population in a cost-effective manner. Most SCD events are due to ventricular arrhythmia in the setting of coronary artery disease [1]. However, approximately 50% of victims of SCD have no previously diagnosed heart disease [2], and recognizably high-risk groups comprise a small proportion of those at overall risk [3,4]. This highlights the tragic nature of SCD, where the presenting event is most often unexpected death, particularly when occurring at a young age. Despite an overall lower risk of SCD compared with men [1,5], women may be more likely to present with SCD as the first manifestation of cardiovascular disease [6]. For example, in a prospective cohort study of 121,701 women between 1976 and 1998, 224 SCDs occurred, and only 31% of the women had known cardiac disease prior to the event [7]. Despite manifest differences in underlying pathophysiology, electrophysiology (EP), mechanisms, and epidemiology of SCD between men and women, risk stratification for SCD is rarely modified by sex.

Risk markers

Age

Older age is the strongest risk factor for SCD, even in those with no previously known cardiovascular disease [8]. The generalized risk increase for individuals over 35 years of age is estimated at 0.1%−0.2% per year [9]. However, this is not a linear relationship, and the most marked increase in risk is seen between the ages of 40−65 years. Conversely, in the setting of advanced coronary heart disease and cardiomyopathy, the progression and severity of the underlying structural heart disease confers a higher SCD risk than age [9].

Cardiovascular disease and coronary artery disease risk factors

Ischemic coronary artery disease is the most common underlying pathology found in individuals who suffer SCD [1]. However, while coronary artery disease is found in 70%−75% of men who experience SCD, the prevalence in women is only 40%−45% [10,11]. Women who suffer an SCD event are less likely to have had a prior diagnosis of either heart failure (odds ratio 0.51; 95% confidence interval 0.31 to 0.84) or coronary artery disease than men (odds ratio 0.34; 95% confidence interval 0.20 to 0.60) [6]. Studies in diverse cohorts have confirmed association of SCD with standard coronary risk factors of diabetes, hypertension, hypercholesterolemia, and chronic kidney disease [7]. In addition to conventional risk factors for cardiovascular disease, a growing body of research suggests that pregnancy, and complications seen during pregnancy, can portend a predilection for adverse cardiac events, including SCD [12,13]. Previously, preeclampsia and gestational diabetes were felt to be conditions just limited to the duration of pregnancy; however, numerous studies now show a conferred continued risk throughout life, including increased cardiovascular mortality [14].

Because of the strong relationship between coronary artery disease and SCD, risk assessment predominantly focuses on broad and modifiable risk factors associated

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with overall cardiovascular health irrespective of sex, such as known coronary heart disease, dyslipidemia, hypertension, obesity, diabetes, and tobacco use. Notably, men and women differ in the underlying pathophysiology of coronary disease; the NHLBI Women's Ischemia Syndrome Evaluation study showed 31% of all cardiovascular deaths occurred in women without obstructive CAD, a condition that is often considered relatively benign [15]. Other described risk factors which may be specific to or more prevalent in women include inflammation, hormonal changes, ovarian dysfunction, hormonal supplementation including oral contraceptives, polycystic ovarian syndrome, preeclampsia, pregnancy-induced hypertension, gestational diabetes, and systemic connective tissue disorders [16].

Ejection fraction

Left ventricular ejection fraction (LVEF) is the cornerstone of SCD risk stratification. Unfortunately, LVEF is neither a sensitive or specific tool to identify those at risk; as LVEF declines, the risk of mortality from both sudden and nonsudden death increases [17,18]. The competing causes of pump failure and other nonsudden deaths result in a declining proportion of arrhythmic deaths in patients with lower LVEF and worse clinical heart failure [19,20]. In the Oregon Sudden Unexpected Death Study, subjects with severely reduced LVEF (≤35%) accounted for 30% of SCD, 22% of subjects had mild to moderately reduced LVEF (36%−54%), and 48% had normal LVEF prior to SCD [21]. Additionally, SCD subjects with normal LVEF were characterized as younger, more likely to be women (47% women, 27% men), with a higher prevalence of CAD, and a higher prevalence of seizure disorder [21]. LVEF is most useful as a tool to identify a high-risk population [2,22], yet no other risk marker has been shown to have better predictive ability [23]. Limitations to the use of LVEF in the use of risk stratification for SCD include measurement variability and inaccuracies, no direct causal relationship between decreased LVEF and arrhythmias, spontaneous variation in LVEF in certain individuals, and lack of sensitivity and specificity for SCD [4,23,24].

Electrocardiographic risk markers

Many differences in the normal electrocardiogram (ECG) are manifest when comparing men and women, as detailed in prior chapters. Overall, women have higher heart rates, a shorter QRS duration, and a longer QT interval [11]. Substantial literature has documented specific ECG abnormalities associated with SCD, but the extent to which these risk markers are specifically applicable to sex differences in women are unclear. Results from a large Finnish study found that women with SCD were more likely to have had a prior normal baseline ECG than men (22.2% vs. 15.3%, $P < .001$), suggesting that traditional prognostic ECG markers may not perform as well in women [25].

QRS duration

Prolonged QRS duration (≥110 ms) is associated with increased mortality in the general population, and intraventricular conduction delay (QRS duration ≥ 110 ms without criteria of complete or incomplete bundle branch block) is associated with increased risk of arrhythmic death [26,27]. In a community-based study, individuals with prolonged QRS duration or intraventricular conduction delay were more often male, with no difference seen between men and women for overall mortality or arrhythmic death [26].

Left bundle branch block

Left bundle branch block (LBBB) has long been associated with increased overall mortality, particularly in the heart failure population, yet it is as related to other heart failure−related adverse outcomes as it is to SCD [28]. In a Finnish population study, LBBB was only weakly predictive of arrhythmic death [26], yet in a large Italian registry, the presence of a complete LBBB was an independent risk factor for SCD in patients with and without congestive heart failure (hazard ratio, 1.58; 95% confidence interval, 1.21 to 2.06)[29]. The study population of 5517 included 1295 women (23.5%), of which 29.3% had an LBBB [29].

QTc

A strong and longstanding association between prolonged ventricular repolarization, usually defined as a prolonged corrected QT interval (QTc) and risk of SCD, is well established [6,30]. The QT interval is longer at resting heart rates in women, likely due to the effects of sex hormones, since this difference is attenuated after menopause [11]. Despite longstanding concern that women have a predisposition to QT prolongation due to drugs, and a resultant predisposition to torsades de pointes, data suggest this effect may be due to a smaller body size and higher drug concentration levels [11,31]. The value of prolonged QTc in predicting SCD has been evaluated in several prospective cohort studies [30,32]. In the Rotterdam study, a QTc interval of >450 ms in men and >470 in women was associated with a threefold increase in risk of SCD (hazard ratio, 2.5; 95% confidence interval, 1.3 to 4.7), after adjustment for clinical and demographic variables [30]. A Finnish prospective observational study of 5869 individuals with SCD noted that the mean QTc duration was relatively similar between women and men (mean 438.2 ms as compared to 439.5 ms, respectively). However, QTc prolongation in men (QTc >450 ms) was

more prevalent (34.4%) than QTc prolongation in women (QTc >470 ms) (17.2%) [25]. A markedly prolonged QTc (>490 ms) was seen equally in both men and women.

Tpeak-tend

The QTc is not always easily measurable due to intraventricular conduction delay or block [33]. The Oregon Sudden Unexpected Death Study evaluated prolongation of the interval between the peak and the end of the T wave (Tpeak to Tend [TpTe] measured in lead V5), which correlates with transmural dispersion of repolarization in the left ventricle, as a risk marker for SCD [33]. Prolongation of the TpTe was associated with SCD independent of sex, age, QTc, QRS duration, and left ventricular dysfunction; lending to measure particular utility in individuals with a normal QTc and in those where QTc calculation is difficult due to intraventricular conduction delay [33].

Early repolarization

Early repolarization, defined as elevation of the J-point junction at the end of the QRS complex and the beginning of ST segment on ECG, is a risk marker for arrhythmias and SCD [34,35]. Horizontal or down sloping J-point elevation of $\geq$2.0 mV in the inferior and lateral ECG leads is associated with a threefold risk of death from cardiac causes or arrhythmia [36]. In this community-based Finnish study of a middle-aged population, 70% were men; however, no differences were seen between men and women in regard to the overall endpoints [36].

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is mechanistically a potential substrate of ventricular arrhythmias due to the development of fibrosis, alterations in action potential duration, conduction, and early afterdepolarization and is a well-described risk marker for SCD [37,38] (Fig. 70.1). LVH is more prevalent in women on ECG compared with men, occurring in 17% of women with SCD and 10.6% of men ($P < .001$) [25]. Additionally, LVH combined with repolarization abnormalities was also more common in women than men (8.2% vs. 4.9%) [25]. A promising line of investigation is whether ECG LVH may convey sex-specific information with respect to risk of SCD that may reflect electrical rather than anatomic remodeling [38].

Atrial fibrillation

Atrial fibrillation (AF) is the most commonly diagnosed arrhythmia and affects approximately >33 million individuals worldwide [39]. AF is associated with an increased risk of stroke, heart failure, dementia, and mortality [40]. This excess mortality was attributed to comorbid conditions in the AF population, until an analysis from the Women's Health Study revealed an independent risk for cardiovascular death associated with new-onset AF, in a healthy population with a low burden of cardiovascular disease [40]. Recent studies have also suggested that AF is an independent risk factor for SCD(41), though the mechanism is not yet fully understood [42]. Analysis of the data from the ENGAGE AF-TIMI for insights into SCD revealed that patients with SCD were predominantly male (70.6%) with persistent or permanent AF (82.9%) [39]. Independent risk factors for SCD were identified as male sex, higher heart rate, LVH, digitalis use, and nonuse of beta-blockers [14]. Sex-stratified analysis was also performed using the ARIC, and CHS studies found the risk of SCD associated with AF in women to be comparable to that in men [41].

Autonomic markers

The autonomic nervous system is crucial in maintaining physiologic hemostasis, and imbalances or alterations cause clinically relevant shifts in cardiac EP [4]. Normal cardiac mechanical and electrical function depends on a balance of sympathetic and parasympathetic tone. In population studies, sinus rate at rest, heart rate during times of mental stress, and rate during and after exercise have been examined for association with SCD risk in several studies [43–45]. The risk of SCD has been found to be elevated for individuals with a high resting heart rate (>75bpm) (relative risk 3.92), limited heart rate increase during exercise (<89 bpm) (relative risk 6.18), or decreased heart rate during recovery after exercise (<25 bpm) (relative risk 2.20 [43]. The mechanistic relationship in humans is unclear; high heart rates may increase myocardial oxygen demand and decrease coronary perfusion, reflect poor levels of physical fitness or overall heath, or may reveal abnormalities of the autonomic nervous system [43]. Women have higher heart rates than men, and similarly to the QT interval, this appears to be related to sex hormone status, since differences are negligible before puberty and after menopause [11].

Cardiac parasympathetic activity tends to be antiarrhythmic, while sympathetic input tends to be proarrhythmic; specific autonomic testing includes both resting evaluation of RR intervals and provocation with maneuvers [44]. Multiple tools have been developed to evaluate the autonomic nervous system, including heart rate variability, baroreflex sensitivity, and heart rate turbulence. Notwithstanding the development of a substantial number of different tests, little comparative data are available to guide testing choice, or interpretation of results. In general,

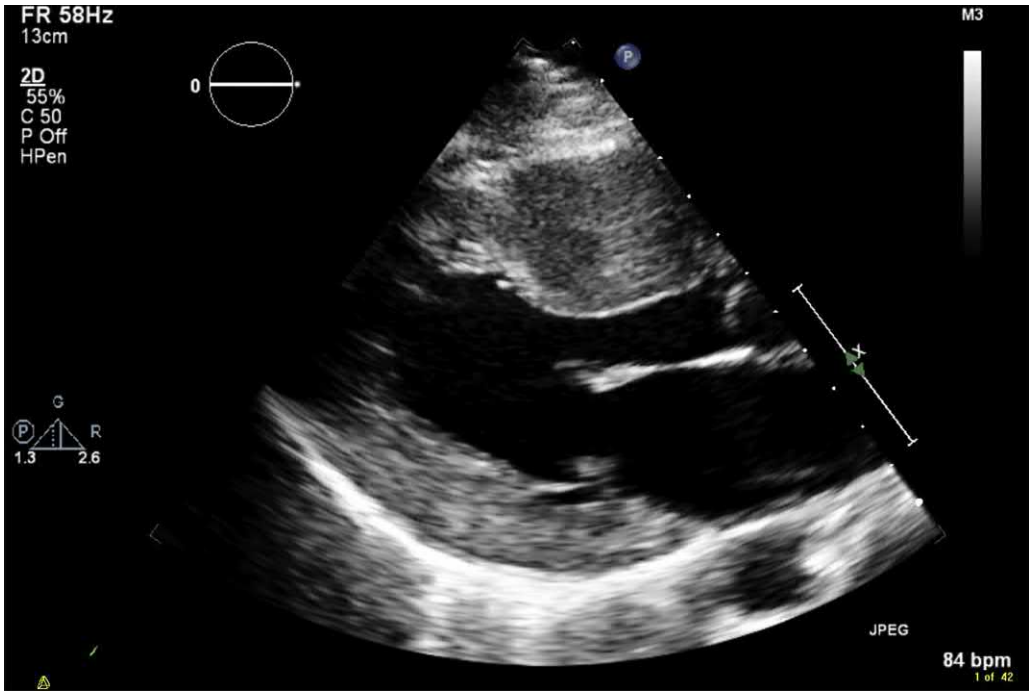

FIGURE 70.1 Transthoracic echocardiogram showing marked concentric left ventricular hypertrophy.

arrhythmic risk has been shown to be increased when markers of vagal activity decrease, or when markers of sympathetic activity increase [4].

MRI imaging

Myocardial fibrosis is associated with ventricular contractile impairment [46], and additionally provides a substrate for reentrant ventricular arrhythmias [47]. Evaluation of patients with dilated cardiomyopathy with late gadolinium enhancement (LGE) on cardiovascular magnetic resonance imaging (MRI) has shown that approximately 30% have midwall LGE, representative of replacement fibrosis(48) (Fig. 70.2). LGE is known to be an important prognostic factor for SCD, conveying important prognostic information in addition to LVEF [48]. A prospective study of 399 patients with dilated cardiomyopathy and LVEF of $\geq$40% found a ninefold increased risk in patients with midwall LGE with a composite of SCD or aborted SCD with no difference between men and women [49]. Earlier studies

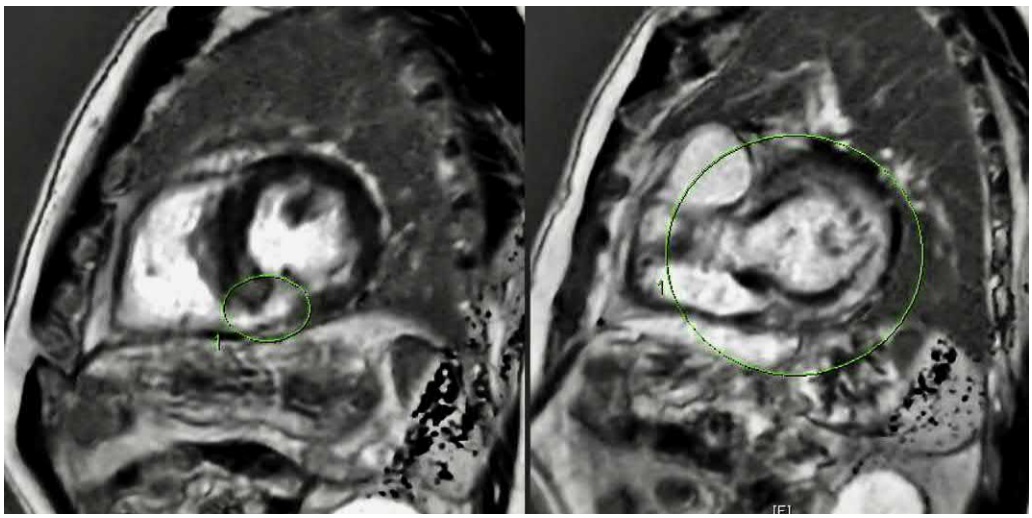

FIGURE 70.2 MRI highlighting areas of late gadolinium enhancement in a patient with a history of sudden cardiac death.

have suggested that patients with midwall LGE are more likely to be male [48]; however, the recent Fingesture study found that patchy myocardial fibrosis seen on autopsy was a more prevalent association with SCD in women (5.2%) than in men (2.6%) [25]. Several systematic reviews and metaanalyses have evaluated the association between LGE and SCD in patients with ischemic and several types of nonischemic cardiomyopathies, revealing a strong association with all-cause mortality, cardiovascular mortality, and SCD [50–53].

Electrophysiology study

Invasive EP testing for risk stratification for SCD consists of programmed ventricular stimulation to evaluate inducibility of sustained ventricular tachycardia or ventricular fibrillation [54] (Fig. 70.3). Risk stratification with EP testing was an important component of the Multicenter UnSustained Tachycardia Trial (MUSTT) trial [55]. Patients with coronary artery disease, LVEF <40%, and nonsustained ventricular tachycardia underwent EP study, and those with inducible ventricular arrhythmia were randomized to standard care or EP-guided antiarrhythmic drug therapy (with progression to implantable defibrillator therapy in this arm) [55]. The subjects in the arrhythmic drug treatment group had improved survival, and subgroup analysis showed this was due to defibrillator therapy [55]. MUSTT remains the largest study to confirm the value of EP testing to identify patients with coronary disease and reduced LVEF at particularly high risk of SCD. However, the negative predictive value is moderate; a rate of cardiac arrest of SCD of 12% at 2 years was seen in MUSTT patients who were noninducible [55].

In a series of nonischemic cardiomyopathy patients who underwent EP testing for risk stratification, 44 of 158 patients had inducible ventricular arrhythmia [56] (Fig. 70.4). Induction of a ventricular arrhythmia was the only independent predictor of defibrillator therapy (hazard ratio, 4.195; $P = .007$; confidence interval, 1.467–11.994) [56]. Similarly, in a mixed diagnosis group of 265 patients with heart disease or syncope, 47.2% were inducible for sustained ventricular tachycardia and 22.6% were inducible for nonsustained ventricular tachycardia [57]. The area under the receiver operating curve for a combined endpoint of SCD or defibrillator therapy was higher for inducibility of ventricular arrhythmias compared with LVEF (0.636, 95% CI: 0.563–0.709 vs. 0.593, 95% CI: 0.515–0.670) and was highest in patients with LVEF >35% (0.681, 95% CI: 0.578–0.785) [57].

Genetics

A familial predisposition to SCD, independent of known inherited arrhythmia syndromes (which are reviewed in other chapters), is well described, particular in the setting of coronary artery disease, the primary cause of SCD [58–60]. Genetic variations that predispose to life-threatening arrhythmia are multifactorial and include alternations in autonomic regulation, repolarization, and other electrical changes in automaticity, conduction, and susceptibility to triggers, in addition to thrombosis and inflammation. Several genome-wide association studies on

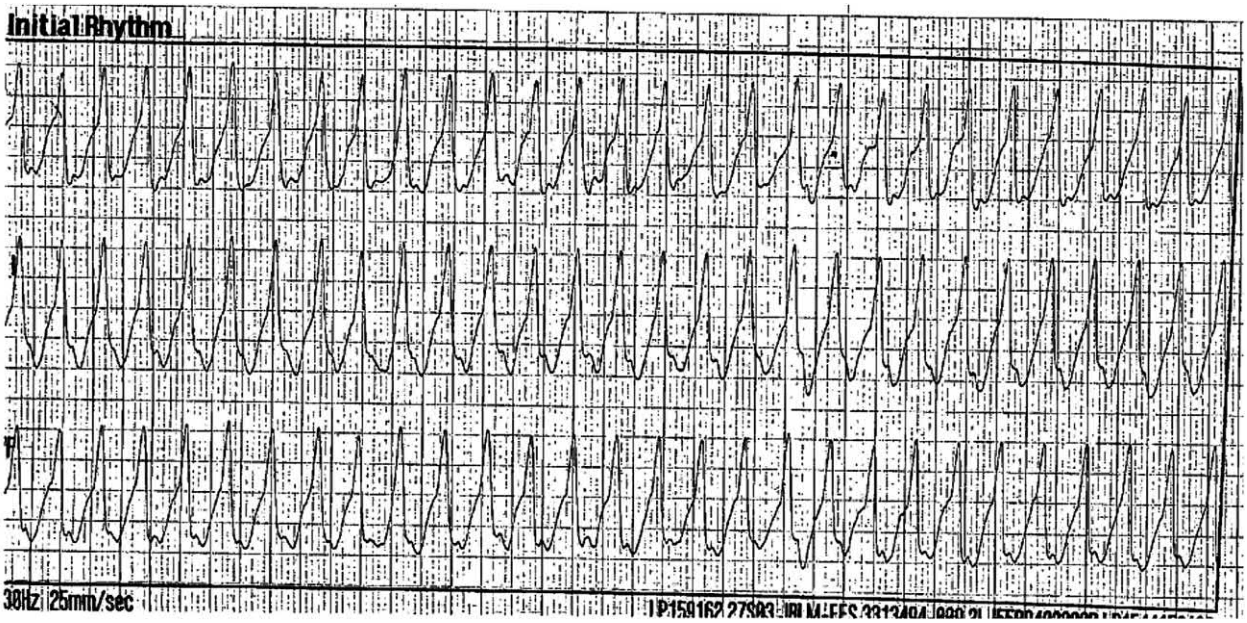

FIGURE 70.3 EMS strips illustrating ventricular tachycardia in the field.

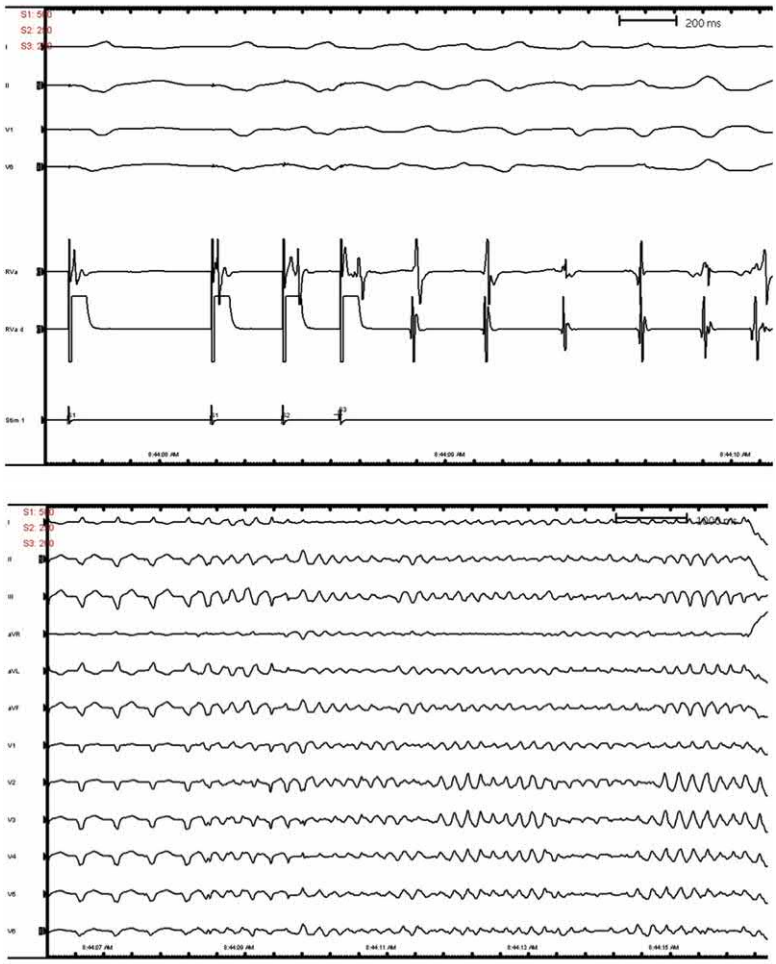

FIGURE 70.4 Electrophysiology study with induced ventricular arrhythmia in patient with nonischemic cardiomyopathy for risk stratification.

SCD have been published, revealing susceptibility loci for ventricular fibrillation and SCD [61,62].

Unique approaches to risk stratification for SCD have been developed for specific types of patients, notably those with inherited arrhythmia syndromes. Genetic screening plays an important role in identification and risk stratification of many of these individuals. Genetic screening has become increasingly important in patients with recognized cardiomyopathy, due to increased recognition of a high risk of SCD unrelated to low LVEF in individuals with mutations in lamin A/C or phospholamban, for example [63]. For comprehensive discussion on the inherited arrhythmia syndromes, please refer to dedicated chapters in this volume.

Malignant mitral valve prolapse

Mitral valve prolapse (MVP) is one of the most common valvular pathologies and affects an estimated 2%–3% of the population. While usually a benign condition, MVP is likely an underestimated cause of arrhythmic SCD, particularly in young women [64,65]. The pathologic causes of myxomatous mitral valve are known to arise from accumulations of proteoglycans leading to thickening of the leaflets, chordal dilation, and annular dilatation. Observations of this pathology in the valve and valve apparatus and their relationship to mitral regurgitation are well understood; however, the exact relationship between MVP and ventricular arrhythmias and SCD is more controversial. Basso and colleagues examined pathologic specimens from 650 individuals under the age of 40 who suffered from SCD [64]. Of the 650, 43 patients with isolated myxomatous MVP with no other underlying cardiac pathology were identified. Of those 43 patients, 26 were female, representing 7% of the entire SCD population and 13% of the women with SCD. Prior ECGs were available in 12 of the 43 patients, and 10 of the 12 showed negative/isodiphasic T waves in the inferior leads, and all of the 12 had prior evidence of RBBB morphology ventricular arrhythmias. Histologic evaluation from the 43 patients showed

increased endoperimysial and patchy replacement fibrosis at the level of the papillary muscles and the adjacent free wall, as well as in the subendocardial−midmural layer of the inferobasal wall [64]. In addition to the pathologic specimens, 30 living patients with known MVP also underwent cardiac MRI, which showed LGE in the papillary muscles in 25 (83%) of the patients, showing evidence of a substrate for electrical reentry in patients with MVP [64]. Based on registry and pathologic studies, young adult women with bileaflet MVP, inferior lead T-wave abnormalities, and frequent premature ventricular contractions are at the highest risk for SCD [64,66]. Overall, the high prevalence of MVP in cohorts with SCD suggests association with life-threatening arrhythmias, possibly mediated by a fibrotic substrate and relative excess of triggers for ventricular fibrillation [25,67].

Risk assessment calculators

A variety of risk assessment tools and predictive models have been developed to aid in identifying individuals at high risk for either SCD or significant cardiovascular events, yet progress have been hampered by the overlap between the phenotype of SCD and other causes of cardiovascular mortality, leading to lack of specificity. Demographic, clinical, laboratory, ECG, and autonomic variables differ across models, and little comparative data exist. Female sex has most often been found to have a protective effect, yet multivariate models do not always include sex, since sex is often not found to be independent of other strong SCD risk factors, particularly age [68].

ACC/AHA CVD Pooled Cohort risk equation

The ACC/AHA Pooled Cohort risk equation was developed in 2013 to provide a 10-year risk estimate for first cardiovascular event (as defined by nonfatal MI, coronary heart disease death, or fatal or nonfatal stroke) in patients free of previously known cardiovascular disease. The risk equation does incorporate sex- and race-specific calculations for overall cardiovascular risk, with women and younger individuals having the lowest 10-year risk [69]. SCD was included in and did comprise a portion of the coronary heart disease deaths; however, there were also other non−SCD-included events as well, likely leading to limitations in the utility of the risk equation specifically for SCD risk prediction [70].

Atherosclerosis Risk in Communities sudden cardiac death prediction model

Deo and colleagues developed an SCD prediction model based on data from participants in the Atherosclerosis Risk in Communities (ARIC) and validated in the Cardiovascular Health Study (CHS) with the specific aim of developing a risk calculator which could be applied to US adults without a known history of cardiovascular disease [68]. Several independent risk factors were identified, including age, male sex, black race, current smoking, systolic blood pressure, hypertension, diabetes, serum potassium, serum albumin, high-density lipoprotein, estimated glomerular filtration rate, and QTc interval [68]. Over a 10-year follow-up, the model showed good to excellent discrimination for SCD (c-statistic 0.820 in ARIC and 0.745 in CHS). This SCD prediction model was noted to outperform the 2013 ACC/AHA CVD Pooled Cohort risk equation for the prediction of SCD [68]. The increased specificity for SCD over cardiovascular mortality may be due to the addition of variables such as potassium, corrected QT interval, and estimated glomerular filtration rate; however, the addition of echocardiographic LVEF did not enhance SCD prediction [68].

Simple community−based risk-prediction score for SCD

Bogle and colleagues utilized the Framingham Heart study to develop and the ARIC study to validate a community-based, 10-year risk SCD prediction score using commonly measured clinic variables, including age, sex, cholesterol, cholesterol and antihypertensive agents, blood pressure, smoking, diabetes, and body mass index [71]. Over a 10-year follow-up, model discrimination was very good to excellent (c-statistic 0.82 in whites, 0.75−0.77 in blacks). Sex-specific scores were derived, but due to the small size of SCD events when stratified by sex, the final model presented a sex-adjusted risk score by race [71].

Seattle Proportional Risk Model

The Seattle Proportional Risk Model was developed as a tool to estimate the proportion of mortality risk due to SCD versus nonsudden death (Fig. 70.5). The model was derived in patients with heart failure without an implantable cardioverter defibrillator [72]. Of 9885 patients included in the study, 2552 deaths occurred during an average follow-up of 2.3 years, and of those, 1225 were classified as SCD [72]. Women comprised 21% of the total cohort and accounted for 15.8% of the SCD group and 21.2% of the nonsudden death group [72]. Lower LVEF and better functional class, younger age, male sex, and higher body mass index were independently associated with a greater proportional risk of SCD [72]. Conversely, diabetes, low or high blood pressure, kidney disease, and hyponatremia were associated with a lower risk of SCD. This model has been validated in several other cohorts and is of clinical use to calibrate the potential benefit of defibrillator therapy [73−75].

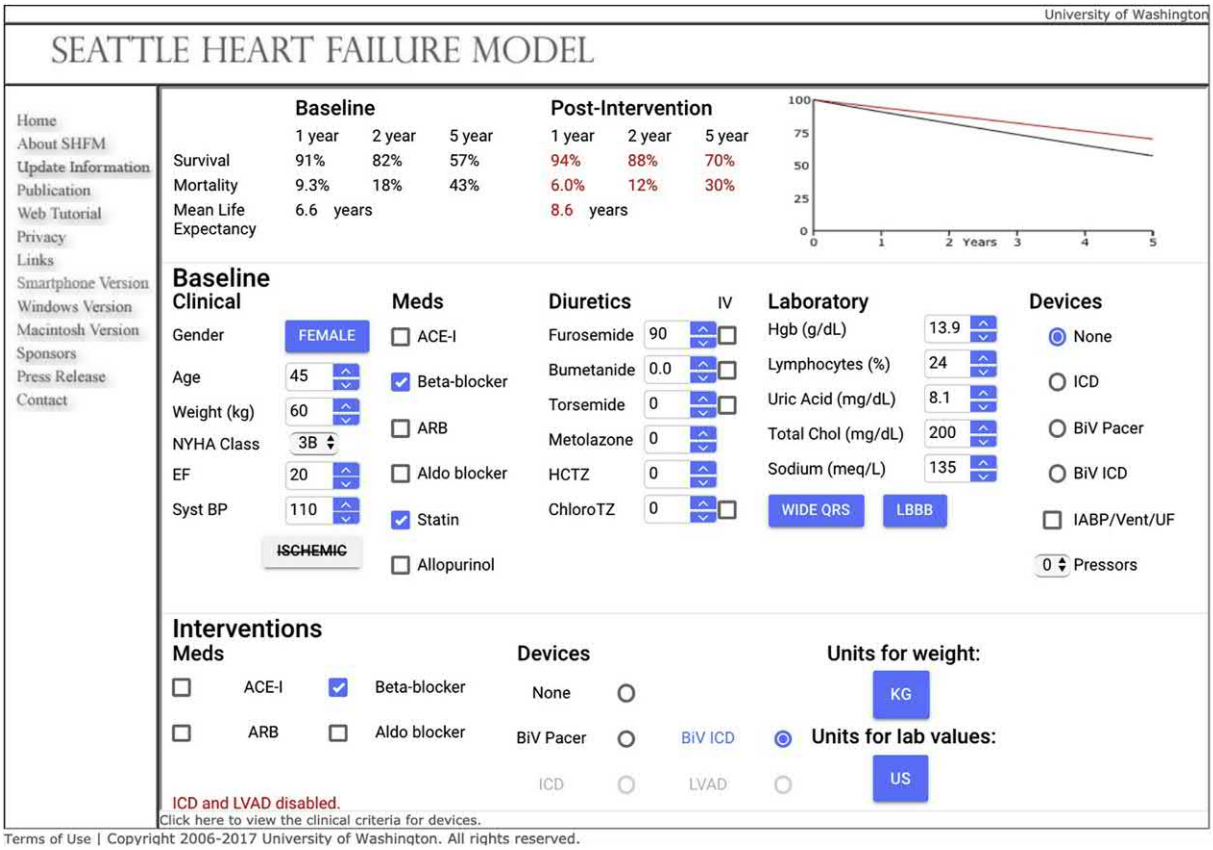

FIGURE 70.5 Example of the Seattle Proportional Risk Model used as a tool to estimate the proportion of mortality risk due to sudden cardiac death versus nonsudden death.

Conclusion

Risk stratification specific to sudden death is a critical issue for improving population health, but progress is hindered by a syndromic definition, and risk markers that overlap with outcomes of heart failure and overall cardiovascular mortality. Given the diversity of underlying diagnoses, it is likely that future advances will depend on further development of risk models incorporating multiple clinical features, including those specific to women. Future research will also require consideration of the declining proportion of comparatively treatable ventricular arrhythmias and increasing incidence of pulseless electrical activity, particularly in women.

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Part XVI

Drug therapy

Материал, защищенный авторским правом

Chapter 71

Safety and efficacy of antiarrhythmic drugs

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Antiarrhythmic medications have been available for over 100 years. While we know there are substantial biological and physiologic differences between women and men, surprisingly few studies have focused on sex differences in efficacy and safety of antiarrhythmic medications. Currently we have a (partial) understanding of some electrocardiographic and (electro)physiological differences, and we are just beginning to elucidate others. This is paramount since heightened awareness of sex differences, and the role of hormonal changes, may have important implications in the clinical management of women with arrhythmias.

Sex differences in pharmacokinetics and pharmacodynamics

Pharmacokinetics

Women and men differ in physiology and body composition, and hence exhibit differences in drug pharmacokinetics [i.e., the way drugs are absorbed, distributed, metabolized, and excreted] and pharmacodynamics [i.e., the response of the body to the drug]. These differences may result in a diverse response to cardiovascular drugs, making it essential to understand, and further explore, sex differences that can affect drug safety and efficacy [1−3].

Sex differences in pharmacokinetics derive from differences in drug absorption, plasma and tissue distribution, metabolizing enzymes and transporters, excretion activity, and hormonal changes (Fig. 71.1). These differences might be especially important in antiarrhythmic drugs with a narrow therapeutic margin [4−6].

It is known that women have a lower gastric acid secretion; consequently, women may have a lower bioavailability of drugs that require an acidic environment for absorption. Women also have slower gastrointestinal transit times, which can diminish absorption of medications such as metoprolol and verapamil [7]. Furthermore, waiting time between meals for drugs that require to be administered on an empty stomach should be longer in women [8,9].

Distribution of drugs in women is influenced by their higher percentage of body fat, lower body weight, lower plasma volume, lower organ size, and lower blood flow. Lipophilic drugs will have a higher volume of distribution and longer effects, while the volume of distribution of hydrophilic drugs will be smaller, reaching higher peak plasma levels with consequently greater effects in women compared to men [2,4]. Therefore, some antiarrhythmic drugs that require loading dosages (e.g., amiodarone and procainamide) may reach higher peak plasma levels and more (adverse) effects in women [10].

Drug metabolism (biotransformation) occurs predominantly in the liver. The main enzymes involved in phase I metabolism belong to the cytochrome P450 (CYP) system. Expression and activity of some CYP isoenzymes show clear sex-related differences (Fig. 71.1) [11,12]. Phase II metabolism processes are generally accelerated in men, causing some medications to clear faster, including digoxin and propranolol [13,14]. Furthermore, increased levels of estrogen and progesterone can alter hepatic enzyme activity. This can result in drug accumulation or decreased drug elimination. The kidney is the major organ of drug excretion. All three major renal functions, glomerular filtration, tubular secretion, and tubular reabsorption, as well as renal blood flow, are generally greater in men than in women. This results in renal clearance being up to 10%−25% lower in, especially older, women [5,6].

Pharmacodynamics

Currently, reported clinical significance of abovementioned sex differences is limited, mainly because women are

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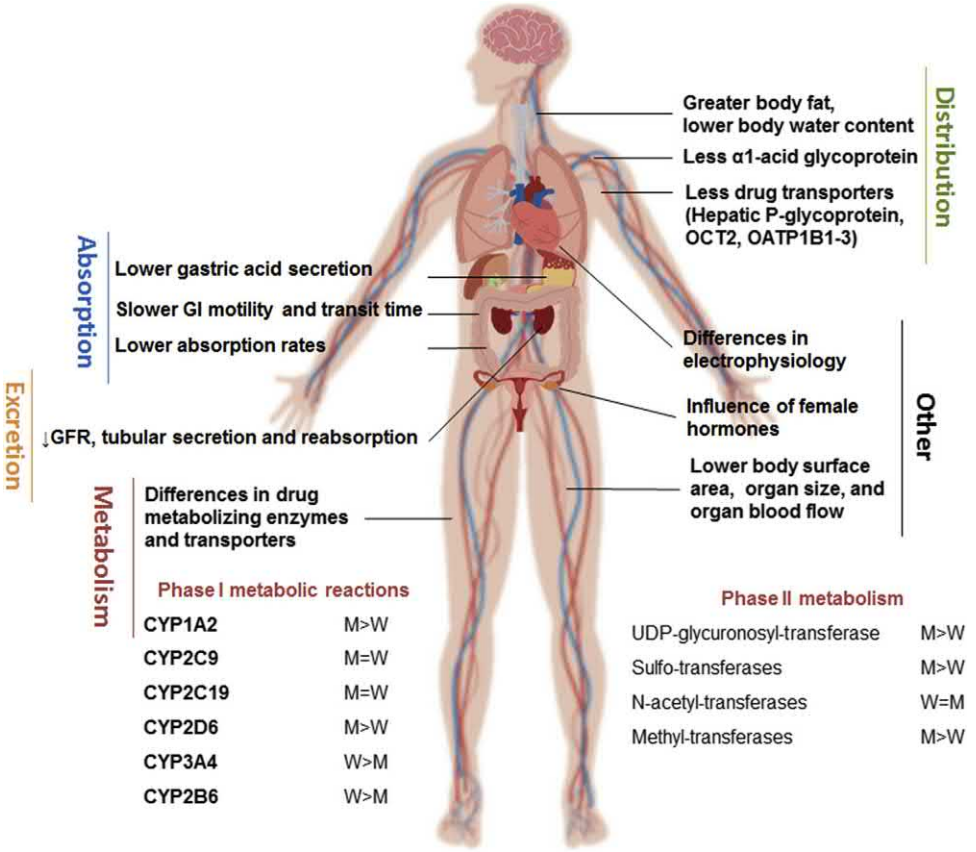

FIGURE 71.1 Differences in pharmacokinetics in women compared to men. Women and men differ in physiology and body composition, and hence exhibit differences in drug pharmacokinetics. The figure shows differences in the way drugs are absorbed, distributed, metabolized, and excreted in women compared to men. *GFR*, glomerular filtration rate; *GI*, gastrointestinal.

underrepresented in clinical trials and sex differences have almost never been studied prospectively. Consequently, efficacy and safety of several widely used cardiovascular drugs is mainly based on post-hoc analyses of clinical trials. Additionally, the potential influence of sex (hormones) on therapeutic response is often not taken into account. Phase I studies are often conducted in young healthy volunteers who differ in their hormonal profile to the men and (post) menopausal women who receive the treatments. Therefore, the appropriate dosage for men *and* women of many (antiarrhythmic) drugs routinely used in clinical practice has not been studied [3]. More insights into therapeutic drug concentrations will help to minimize therapeutic adverse events and enhance therapeutic effectiveness.

Sex differences in electrophysiology of the heart

It has been known for long that sex-based differences exist in cardiac electrical activity, an observation first described by Bazett at the beginning of the 20th century when he wrote "It has only been possible to collect a few figures for normal women, but so many of these fall outside the range for normal men" [15]. Over the last decades several electrophysiological properties were found to be affected by sex [16–18]. Women have enhanced sinoatrial node activity, shorter sinus cycle length, and shorter sinus recovery time compared to men, especially during pregnancy [19,20]. Women also have enhanced atrioventricular node function, with shorter atrioventricular node effective refractory period. Furthermore, they exhibit faster infra-Hisian conduction, and longer ventricular action potential duration [18,20,21]. The standard 12-lead electrocardiogram reflects these differences with most notably a higher heart rate at rest, shorter PR interval, shorter QRS duration, and a more prolonged corrected QT (QTc) interval in women (Fig. 71.2).

The higher heart rate in women appears to be related to intrinsic properties of the sinus node and is further influenced by the autonomic nervous system and hormonal effects [19,22]. In both men and women, the QRS duration gradually lengthens from birth, but starting from adolescence the QRS width becomes significantly longer in men, a difference that persists after correction for body weight and cardiac mass [23].

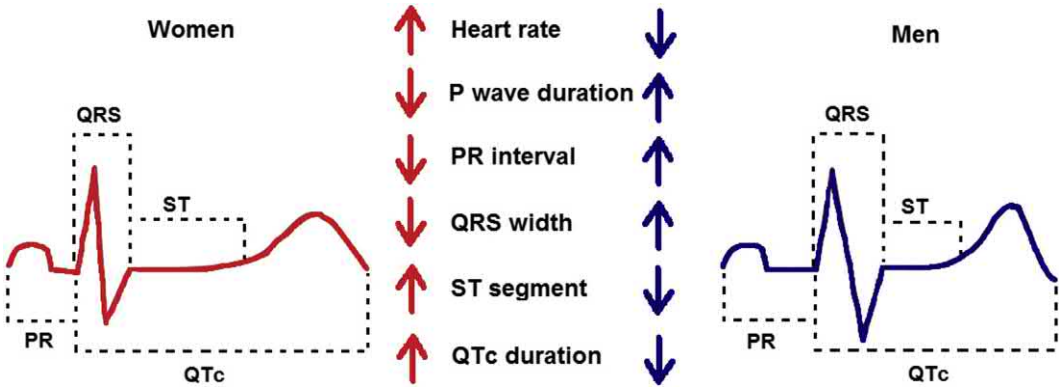

FIGURE 71.2 **Most prominent cardiac electrophysiology sex differences.** Women have a faster heart rate, shorter P-wave duration, shorter PR interval, shorter QRS width, increased ST segment duration, and increased corrected QT-interval duration (QTc).

QTc interval is notably longer in women (approximately 10–20 ms), independent of autonomic modulation. This difference is not observed in the prepubertal phase, but starting from puberty, male individuals manifest QTc shortening, whereas QTc intervals in women remain stable or even slightly increase [18,24,25]. Throughout life, as testosterone levels decrease in men, the QTc gradually increases [26]. In elderly men and women, the difference in QTc interval diminishes and becomes negligible [27]. The observation that part of the differences develop in the postpubertal phase suggests a role for sexual hormones, which is also emphasized by the fact that the observed changes are inversely related to testosterone levels in men [28]. In addition, several experimental studies in a variety of (animal) models provide evidence that estrogen increases the QTc interval, while testosterone and progesterone shorten QTc through their influence on a variety of cardiac potassium and calcium channels (Fig. 71.3) [29–36]. However, extensive human data are missing and the exact (hormonal) mechanisms that influence sex differences in arrhythmia pathophysiology remain far from being understood.

Sex differences in the epidemiology of arrhythmias

Well-known sex differences exist in the incidence of several common arrhythmias. Some of the observed differences are related to differences in the frequency of underlying heart disease, such as incidence of coronary artery disease and resultant ventricular tachycardia and ventricular fibrillation in men versus hypertension with left ventricular hypertrophy and diastolic dysfunction in women [37]. Additionally, several factors besides disease occurrence such as treatment referral, interpretation of women's symptoms, and time to treatment influence the reported prevalence of arrhythmias in women and men. The latter clearly warrants further investigation [3].

Overall, women have a higher prevalence of atrioventricular nodal reentrant tachycardias and focal automatic tachycardias, while manifest and concealed accessory pathways with and without atrioventricular reentrant tachycardia have a greater prevalence in men (Table 71.1) [38–42].

Arrhythmias during the ovarian cycle and pregnancy

Due to a cyclic variation in the QT interval, women's susceptibility to arrhythmias varies (Fig. 71.4) [18,43–45].

Changes in estrogen and progesterone concentrations effect potassium-repolarizing currents; increasing estrogen–progesterone ratio's during the follicular phase decrease repolarizing currents, prolong action potential duration and QTc interval, which subsequently increases the risk of Torsades de Pointes. During the luteal phase of the menstrual cycle, when there is a fall in estrogen levels and a rise in progesterone levels, supraventricular tachyarrhythmias are observed more frequently [44,46,47].

During pregnancy women experience an increase in heart rate which is accompanied by reduced heart rate variability and QTc-interval lengthening [48]. Overall, 1%–4% of women without structural heart disease will present with arrhythmias, mostly supraventricular, during pregnancy [49,50].

Sex differences in adverse drug reactions

Antiarrhythmic drugs remain a cornerstone in the treatment of cardiac arrhythmias. While efficacy of class I and III antiarrhythmic medications appear to be similar in women and men, the risk of adverse effects, most notably drug-induced proarrhythmia, is not. Women are at higher risk of adverse drug effects, and, importantly, when they occur

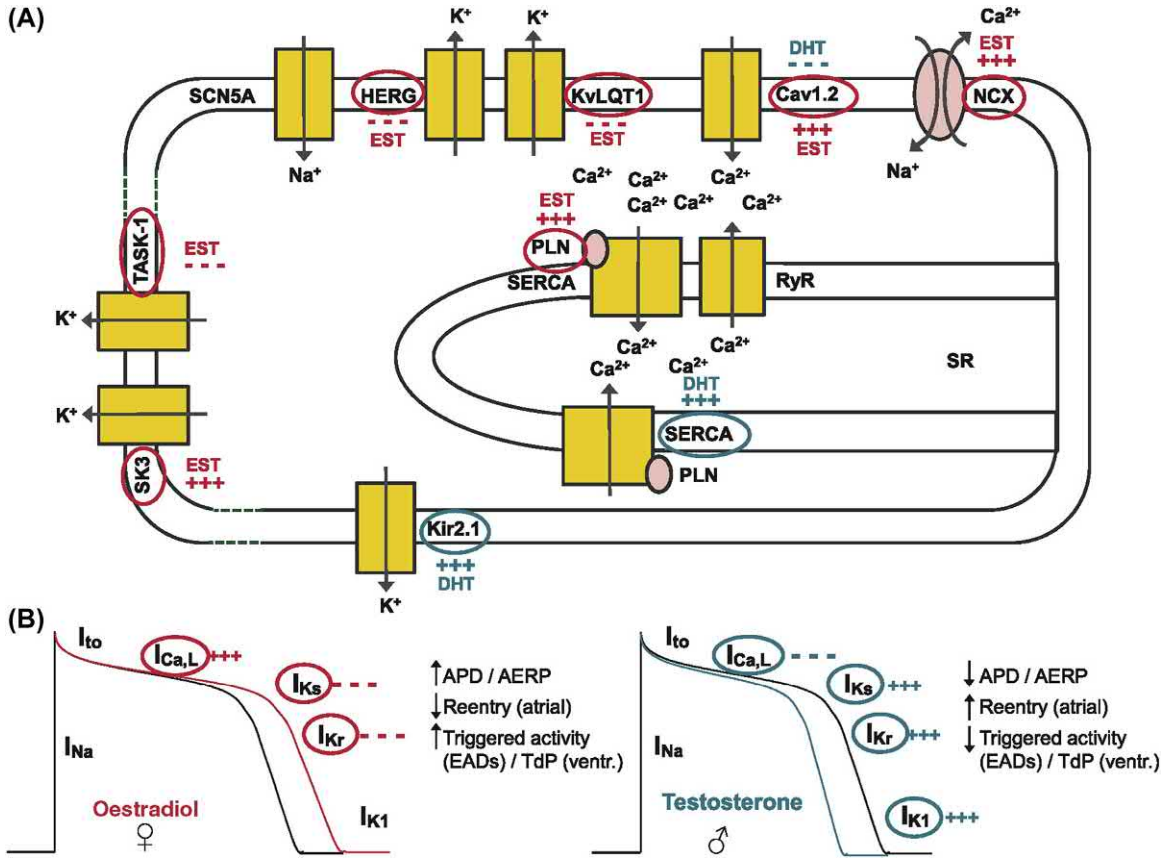

FIGURE 71.3 Sex hormone effects ion cardiac ion channels and currents (A) Schematic figure indicating sex hormone effects on cardiac ion channels/currents and calcium handling proteins in cardiomyocytes. Effects on ion channels that have thus far only been demonstrated in noncardiac tissues are indicated in the left corner separated by green dotted lines. Estrogen-induced changes are color-coded in red, testosterone-induced changes in turquoise. (B) Illustration of resulting effects on cardiac repolarization and arrhythmogenic mechanisms. - - -, reduction; + + +, increase; ↑, increase/prolongation, ↓, decrease. *Reproduced from Odening KE, Deiss S, Dilling-Boer D, Didenko M, Eriksson U, Nedios S, et al. Mechanisms of sex differences in atrial fibrillation: role of hormones and differences in electrophysiology, structure, function, and remodelling. Europace March 1, 2019;21(3):366–376.* AERP, *atrial effective refractory period;* APD, *action potential duration;* DHT, *testosterone;* EAD, *early afterdepolarization;* eNOS, *endothelial nitric oxide synthase;* EST, *estrogen;* IL, *interleukin;* PAI *1, plasminogen-activator inhibitor 1;* SR, *sarcoplasmic reticulum;* TdP, *Torsade de Pointes;* HERG/I_{Kr}, *alpha-subunit to repolarizing delayed rectifier potassium current IKr;* KvLQT1/I_{Ks}, *alpha-subunit to repolarizing slow delayed rectifier potassium current IKs, Kir2.1/*I_{K1}; SCN5A/I_{Na}, *alpha-subunit to depolarizing sodium current INa;* Cav2.1/$I_{Ca,L}$, *alpha-subunit to L-type calcium current ICa,L;* SK3, *small-conductance calcium-activated potassium channel;* TASK-1, *two-pore domain potassium channel;* TNF, *tumor necrosis factor;* VGEF, *vascular endothelial growth factor.*

they tend to be more severe than in men [2,5,51,52]. Reasons may include a higher sensitivity in women, drug–drug interactions, a higher risk of overdosing in women, genetic vulnerability, and hormonal mechanisms (Table 71.2).

The prolonged QTc in women, even more pronounced when taking QT-prolonging drugs ([53,54]), and the higher occurrence of congenital long QT syndrome in women ([55,56]) are associated with an increased risk of Torsades de Pointes [53], even despite equivalent serum concentrations [57]. Causes for this are multifactorial and will partially be influenced by sex and hormonal differences as mentioned earlier. Women show lower levels of expression of several potassium channels and thus have a smaller repolarization reserve [33]. Additionally, estrogen-dependent downregulation of delayed rectifier K^+ (I_{Kr}) currents in the follicular phase of the ovarian cycle prolong QTc and favor early after depolarizations and Torsades de Pointes.

Risk of proarrhythmia and bradyarrhythmia

The risk of proarrhythmia differs among class III agents, with sotalol, dofetilide, and ibutilide having a higher risk of Torsades de Pointes than amiodarone and dronedarone (Table 71.3) [58–66]. Sotalol, dofetilide, and ibutilide are mainly voltage-dependent rapid potassium current blockers, while amiodarone and dronedarone have more diverse pharmacological targets [67,68]. This broad range in electrophysiological properties likely results in a lack of

TABLE 71.1 **Sex differences in the epidemiology of (supra)ventricular arrhythmias.**

Arrhythmia	Women predominance	Men predominance
Bradyarrhythmia	Sinus node disease	Atrioventricular block Carotid sinus syndrome
Supraventricular tachycardia	Inappropriate sinus tachycardia AVNRT	Premature atrial contraction AF AVRT WPW syndrome
Ventricular tachycardia	Congenital LQTS Acquired LQTS Torsades de pointes	Premature ventricular contraction VT SCD Brugada syndrome

AF, atrial fibrillation; *AVNRT*, atrioventricular node reentry tachycardia; *AVRT*, atrioventricular reentry tachycardia; *LQTS*, long QT syndrome; *SCD*, sudden cardiac death; *VT*, ventricular tachycardia; *WPW*, Wolf–Parkinson–White.

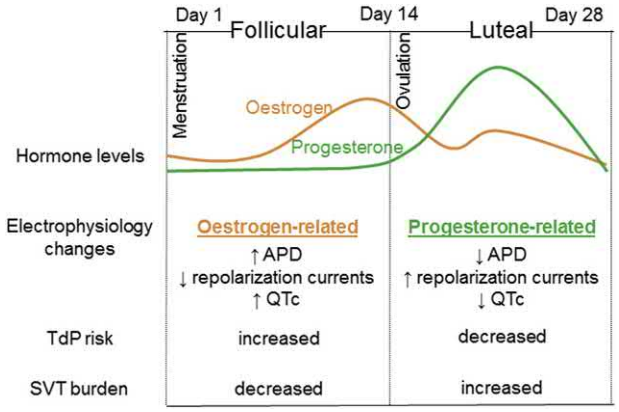

FIGURE 71.4 **Electrophysiological changes and arrhythmia susceptibility during the ovarian cycle.** During the follicular phase, women are at increased risk of Torsades de Pointes. During the luteal phase, they are at increased risk of supraventricular arrhythmia's. *APD*, action potential duration; *SVT*, supraventricular tachyarrhythmia's; *TdP*, Torsades de Pointes.

reverse-use–dependent proarrhythmia, and a more uniform prolongation of the QT interval without QT dispersion, and consequently a low proarrhythmic risk, in contrast to sotalol and dofetilide ([69]).

Sotalol and dofetilide

The Survival with Oral d-Sotalol (SWORD) trial(58) tested the hypothesis that prophylactic administration of oral d-sotalol, a class III antiarrhythmic agent that is a pure potassium channel antagonist (I_{Kr}) without β-blocking activity, would reduce mortality in patients with myocardial infarction and left ventricular ejection fraction ≤40%. The observed increased mortality in the treatment arm caused the trial to be discontinued. Compared to placebo, d-sotalol was associated with a 4.7-fold increased risk of death in women (95% confidence interval (CI) 1.4–16.5) and a 1.4-fold increased risk in men (95% CI 1.0–2.1). The excessive d-sotalol–associated mortality risk was predominately

TABLE 71.2 **Possible reasons for adverse drug reactions in women.**

Reason	Mechanism	Factors
Higher rate of polypharmacy in women (including over-the-counter and herbal medications)	Drug–drug interactions	Drug–drug induced alterations Alterations in pharmacokinetics Alterations in pharmacodynamics
Higher sensitivity in women	Pharmacodynamics	Sex differences in drug targets: i. Receptor number ii. Receptor binding iii. Signal transduction pathway
Higher risk of overdosing in women	Pharmacokinetics	Sex differences in i. Smaller volume of distribution ii. Lower free fraction of drugs iii. Differences in transport, phase 1, and phase 2 metabolism iv. Slower clearance
Possible higher hormonal risk in women/protection in men	Sex hormonal mechanisms	Lower androgen levels and higher estrogen levels, associated with prolonged QTc duration

TABLE 71.3 Estimations of Torsades de Pointes (TdP) risk of several antiarrhythmic drugs.

Drug	Class	Pharmacological targets (67,68)	ECG manifestations	Drug half-life	TdP risk total population (%)	Increased risk in women
Quinidine	IA	I_{Na}, I_{to}, I_{Kr}, I_{Ks}, I_{K1}, I_{KATP}, and I_{Ca} antagonism. In addition autonomic α-adrenergic and cholinergic effects.	↑ QT (not dose related) ↑ QRS (high dose)	8 h	±1.0	5x* [66]
Sotalol	III	I_{to}, I_{K1}, and I_{Kr} blocker. In addition β-adrenergic effects.	↓ Sinus rate, may ↑ PR ↑ QT (dose related)	8 h	±2.5	3–4x [59,60]
Dofetilide	III	Considered "pure" I_{Kr} blocker	↑ QT (dose related)	6–10 h	±3.0	3x [61]
Ibutilide	III	I_{Kr} antagonism and I_{Na} activation	↑ QT (dose related)	6 h	±4.0	2x [62]
Amiodarone	I, II, III, IV	I_{Kr}, I_{Ks}, I_{Na}, I_{Ca}, I_{KACh}, I_{to} blocker, α- and β-receptor antagonist.	↓ Sinus rate, ↑ PR ↑ QRS, ↑ QT	~50 days	<1.0	2x [63]
Dronedarone	I, II, III, IV	I_{Kr}, I_{Ks}, I_{Na}, I_{Ca}, I_{KACh} blocker, α-, and β-receptor antagonist.	↓ Sinus rate, ↑ PR	13–19 h	~0	No increased risk in women [64,65]

I_{Ca}, voltage-dependent Ca^{2+} current; I_{KACh}, acetyl-choline sensitive muscarinic K^+ channel; I_{KATP}, ATP-sensitive potassium channel; I_{Kr}, voltage-dependent rapid K^+ current; I_{Ks}, voltage-dependent slow K^+ current; I_{K1}, inward rectifier potassium channel; I_{Na}, voltage-dependent Na^+ current; I_{to}, complex components of transient inward curren. *No Torsades de Pointes observed in men, 5% in women (N = 2).

classified as presumed arrhythmic, but little objective data support this assumption [60]. An analysis of data from 3100 patients of 22 clinical trials taking oral d,l-sotalol showed a threefold increase in the risk of Torsades de Pointes in women compared with men [53]. Fig. 71.5 illustrates the effect of dose and kidney function of d,l-sotalol (Fig. 71.5) [70].

The Danish Investigations of Arrhythmia and Mortality On Dofetilide (DIAMOND) study group performed a double-blind, randomized trial in patients with congestive heart failure (762 patients on dofetilide, 756 patients on placebo) to investigate whether dofetilide affects survival or morbidity [61]. Overall, a reduction in the incidence of Torsades de Pointes during the first 3 days of therapy was observed after adjusting the dose according to renal function (from 4.8% to 2.9%). Nevertheless, female sex was found to be significantly associated with the occurrence of Torsades de Pointes (odds ratio 3.2). No adverse effect, however, on mortality was observed for both sexes [61].

Amiodarone and dronedarone

Amiodarone has been compared with dronedarone, sotalol, and propafenone and was found to be more effective in maintaining sinus rhythm. But its myriad of toxicities frequently limits its use, although risk of Torsades de Pointes is low [63]. Dronedarone, which has reduced interactions with thyroid physiology, decreased affinity in a lipid environment, and a shorter half-life, overcomes many of these side effects [71]. In the Canadian Trial of Atrial Fibrillation (CTAF), amiodarone was compared to sotalol or propafenone for the maintenance of sinus rhythm [72]. Recurrence of AF occurred less frequently in the patients receiving amiodarone (35%) than those receiving sotalol or propafenone (63%, $P < .001$). However, amiodarone users were more likely to discontinue their drug due to adverse events, mainly gastrointestinal and central nervous system symptoms. One patient receiving propafenone experienced a cardiac arrest due to Torsade de Pointes requiring resuscitation [72].

The Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) who randomly assigned persistent atrial fibrillation patients to amiodarone, sotalol, or placebo found that amiodarone was superior for maintaining sinus rhythm, being six times as effective as sotalol in the intention-to-treat analysis [73]. One case of Torsades de Pointes occurred in the sotalol group. With the exception of a slightly higher risk of minor bleeding episodes in the amiodarone group, no significant differences in the rates of adverse events or death were observed [73].

DIONYSOS, a randomized, double-blind trial, evaluated efficacy and safety of dronedarone 400 mg bid versus amiodarone for the maintenance of sinus rhythm in patients with AF. More patients randomized to dronedarone had a

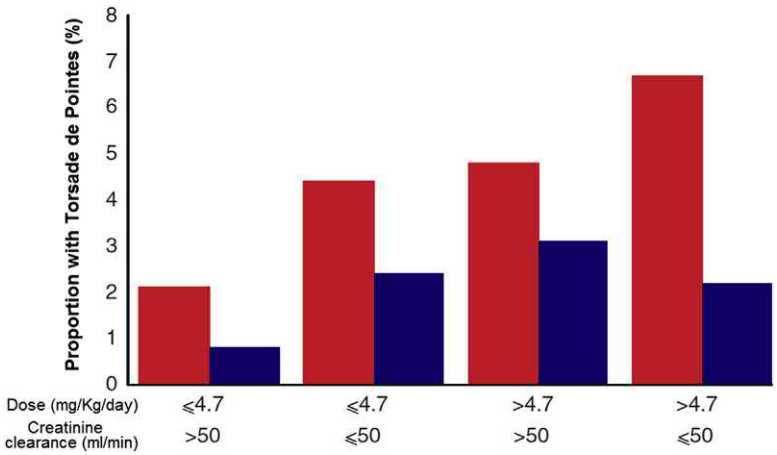

FIGURE 71.5 **Prevalence of Torsade de Pointes by sex.** Four patient subgroups are shown based on d,l-sotalol dose (mg/Kg/day) and creatinine clearance (mL/min). Women = red, men = blue. *Reproduced from data of Coughtrie AL, Behr ER, Layton D, Marshall V, Camm AJ, Shakir SAW. Drugs and life-threatening ventricular arrhythmia risk: results from the DARE study cohort. BMJ Open October 16, 2017;7(10):e016627-2017-016627*

recurrence of AF than patients receiving amiodarone (HR 1.59; 95% CI 1.28−1.98, $P < .001$). Zero patients developed Torsades de Pointes [65]. In ATHENA, a placebo-controlled, double-blind trial that assessed the efficacy of dronedarone 400 mg bid found that dronedarone significantly reduced cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. Bradycardia and QT-interval prolongation were more common in the dronedarone group. One woman and no men receiving dronedarone developed Torsades de Pointes [64].

Bradyarrhythmias

Most of the adverse drug effects observed in the Rate Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) trial, which randomized patients to rate or rhythm control (class IC agents, sotalol or amiodarone), occurred in women who were randomized to the rhythm arm. The occurrence of adverse effects of antiarrhythmics and pacemaker implantations was related to female sex (adjusted HR 4.8; 95% CI 1.2−18.8, $P = .02$), hypertension (adjusted HR 9.0; 95% CI 1.1−71.6, $P = .04$), and amiodarone use (adjusted HR 5.8; 95% CI 1.7−19.5, $P = .004$) [74]. Adverse effects of antiarrhythmic drugs in female patients included sick sinus syndrome (n = 7), Torsades de Pointes (n = 1), and rapid atrioventricular conduction during atrial flutter (n = 1). Pacemaker implantation in women were performed after atrioventricular node ablation for intolerable symptoms (n = 3) and for sick sinus syndrome unmasked by cardioversion (n = 4).

Results from the Fibrillation Registry Assessing Costs, Therapies, Adverse Events and Lifestyle (FRACTAL) registry also showed that bradyarrhythmias (mainly sick sinus syndrome and atrioventricular block) requiring pacemaker implication occurred more often in women than men taking amiodarone for AF [75].

Recommendations for antiarrhythmic drug use

Women treated with class IA or III antiarrhythmic drugs should be aware of the risk and symptoms associated with Torsades de Pointes and institution and continuation of antiarrhythmic drugs should be carefully instituted. The recent publication by Linde et al. provides several practical recommendations (Table 71.4) [1].

To prevent Torsades de Pointes careful monitoring of the QT interval, especially during night when the heart rate is slower, and potassium and magnesium levels, especially during initiation, helps to reduce the risk of proarrhythmia. Polypharmacy with multiple potassium antagonists and unmonitored drug formulation changes should be avoided. With the greater risk of QT prolongation and Torsades de Pointes from not only a variety of nonantiarrhythmic medications, including clopidogrel, furosemide, but also several psychotropics, antidepressants, anticonvulsants, anticancer, and antibiotics, caution should be taken when prescribing such medications in women [57].

Future directions: precision medicine for women and men

It is without a doubt that sex differences exist for multiple aspects of cardiac arrhythmias: from incidence and treatment to sex differences in pharmacokinetics, pharmacodynamics, electrophysiological properties of the heart, management, and potential drug side effects. And while our understanding of these differences is expanding, current knowledge is still inadequate. Sex differences deserve more attention, not in the least to characterize and determine their role so that our assessment and treatment of patients has a foundation that incorporates sex differences if necessary. This requires ensuring adequate representation of women in future clinical trials and sex-specific analyses in the design

TABLE 71.4 Consensus recommendation for antiarrhythmic drug therapy in women(1).

Consensus recommendation	Level of recommendation
Women treated with AADs should be periodically evaluated to confirm their eligibility for AAD treatment [76].	Recommended/indicated
Women with heart failure or pathological left ventricular hypertrophy should be offered amiodarone. Other AAD should be avoided [76].	Recommended/indicated
In women 24-h Holter monitoring during initiation of class III AAD, and 1−2 weeks after dosage increase, should be considered to monitor heart rate and QT prolongation.	May be used or recommended
In women with long-term class III AAD ECG should be performed yearly to monitor heart rate and QT prolongation.	May be used or recommended
Class IA or III AAD should not be instituted in women with a prolonged QT interval (>500 ms), or those with a significant sinoatrial node disease or atrioventricular node disease without a functioning permanent pacemaker.	Should not be used or recommended

AAD, antiarrhythmic drug.

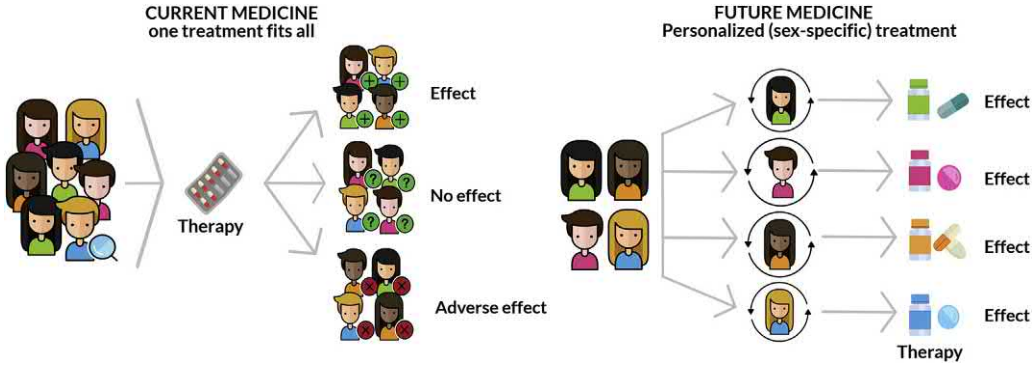

FIGURE 71.6 Paradigm shift in clinical management. From a general "one treatment sits fits all" approach (left) where medications are prescribed to a whole patient group to personalized precision medicine (right) where the patient is central and sex differences are incorporated in assessment and treatment.

of impending studies to better understand the mechanisms by which sex differences exist in cardiac arrhythmias. Furthermore, it is important to consider whether dosages are given on an mg/kg basis or irrespective of body weight; dosing regimens for common and uncommon drugs in women should not simply apply dose−response data measured only in men. Advancing our knowledge will ultimately allow better clinical management of the whole patient population, women included, since it is unlikely that "one treatment simply fits all" (Fig. 71.6).

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Chapter 72

Sex differences in drug-induced QT prolongation

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Introduction

Drug effects are the most common cause of acquired long QT syndrome. A diverse set of cardiac and noncardiac drugs can cause QT prolongation and provoke a fatal polymorphic ventricular arrhythmia called torsade de pointes (TdP) [1,2]. The mechanism of acquired long QT syndrome is through prolongation of the action potential duration by inhibition of the outward delayed rectifier potassium currents I_{Kr} and I_{Ks} and/or enhancement of the inward currents I_{Na} and I_{CaL} [3] during ventricular repolarization. Most drugs that cause TdP block I_{Kr} and prolong the QT interval on the surface electrocardiogram (ECG). Unexpected QT prolongation and TdP caused by noncardiac drugs prompted international regulatory agencies to remove 10 drugs from the market between 1990 and 2006 [4]. Since then, the potential of noncardiac drugs to prolong the QT interval and cause TdP has been a major safety concern in drug development. Two international guidelines were adopted to characterize whether an investigational product has the ability to delay ventricular repolarization, prolong the QT interval, and cause TdP during the development phases of new drugs. The ICH S7b guideline describes the nonclinical testing strategy to assess whether a test substance and its metabolites delay ventricular repolarization [5]. The ICH E14 guideline describes the thorough QT study conducted in healthy subjects as the primary method to assess the potential of a new drug to prolong the heart rate corrected QT (QTc) interval [6].

In clinical trials, QT prolongation is used as a surrogate marker for the risk of TdP. The ICH E14 guideline proposes that drugs with mean increases in the QTc <10 ms have low risk of inducing TdP and drugs that prolong the QTc interval >20 ms are generally thought to be torsadogenic. For drugs that increase the QTc interval >10 ms but ≤ 20 ms, the TdP risk is unknown and intensive ECG monitoring in the targeted patient population is used to assess whether patients or specific subgroups of patients will experience excessive QT prolongation (e.g., QTc >500 ms) in late-stage clinical trials. The torsadogenic potential of drugs, however, is variable even for drugs with similar extent of QT prolongation. Some drugs seem to induce TdP when used alone, yet other drugs seem to induce TdP only in the presence of clinical risk factors such as bradycardia, hypokalemia, high drug concentrations, ion channel polymorphisms, and structural heart disease [1].

Female sex is a powerful predictor of the risk of TdP in patients with drug-induced QT prolongation. Drugs that prolong QTc cause TdP more frequently in women than men [7–9]. Makkar and colleagues performed a retrospective review of literature reports of cardiac drugs with TdP cases from 1980 to 1992 [7]. Women made up 70% of the 332 reported cases of TdP. Similarly, Bednar and colleagues performed a retrospective review of literature reports of patients taking noncardiac drugs who had TdP from 1966 to 2000 [8]. The study found 67% of the 189 cases of TdP occurred in women which is similar to the 70% incidence of TdP reported for cardiac drugs. In clinical trials of antiarrhythmics, the incidence of TdP in women is higher compared to men (Fig. 72.1). After adjusting for other risk factors, women taking d,l-sotalol had threefold the odds of developing TdP compared with men, and the sex difference in TdP risk was age independent and could not be explained by differential dose-related bradycardic responses [10]. Likewise, women taking azimilide had twofold the odds of developing TdP after adjusting for age,

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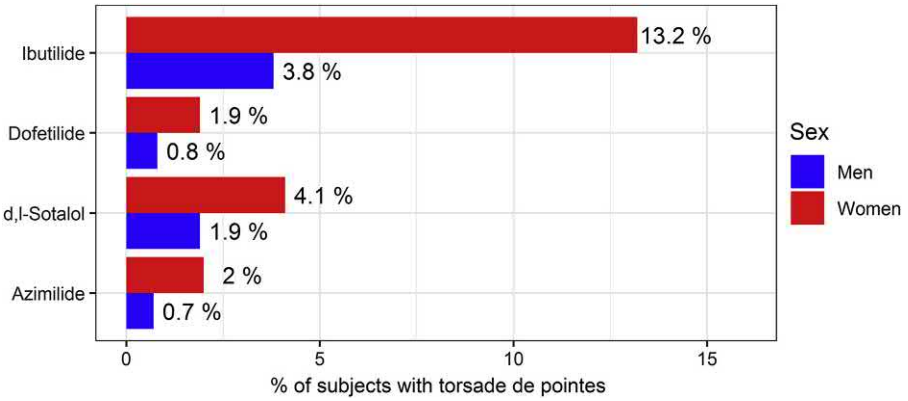

FIGURE 72.1 Higher incidence of torsade de pointes in women (red) versus men (blue) taking d,l-sotalol [10], ibutilide [74], azimilide [11], and dofetilide [75].

diuretic, and aspirin use [11]. Johannesen and colleagues developed a quantitative risk model for TdP using pooled data from 42 clinical trials of four antiarrhythmic drugs to assess the relationship between QTc prolongation and TdP [12]. Women taking antiarrhythmic drugs had twice the odds for developing TdP after adjusting for on-treatment average QTc values and congestive heart failure (Fig. 72.2). Potential factors that could explain the higher rate of TdP in women include longer QTc interval in women due to increased drug exposures, elevated QTc at baseline, or a higher sensitivity to QTc prolonging drugs. Each of these factors and its contribution to longer QT intervals in women is discussed below.

Pharmacokinetic differences between women and men

Pharmacokinetics is the science linking drug dosing with the time course of concentration in the human body. Differences in pharmacokinetics can lead to higher drug concentrations and longer retention in the body because women on average have smaller body size compared to men resulting in smaller distribution volumes and slower total clearance of most medications [13,14]. These pharmacokinetic parameters are affected by body weight according to allometric-based models [15,16]. The administration of fixed doses of medications can lead to increased susceptibility to adverse events in women [17]. For example, women have approximately 40% higher observed maximum moxifloxacin concentrations compared to men following 400-mg moxifloxacin oral doses in thorough QT studies and body weight alone explained these observed differences [18]. Female sex was associated with dofetilide medication discontinuations or dose reductions when compared with men of matched age and renal function [19]. These observations could indicate higher dofetilide concentration in women because a pharmacokinetic analysis showed that women have approximately 14%–22% greater

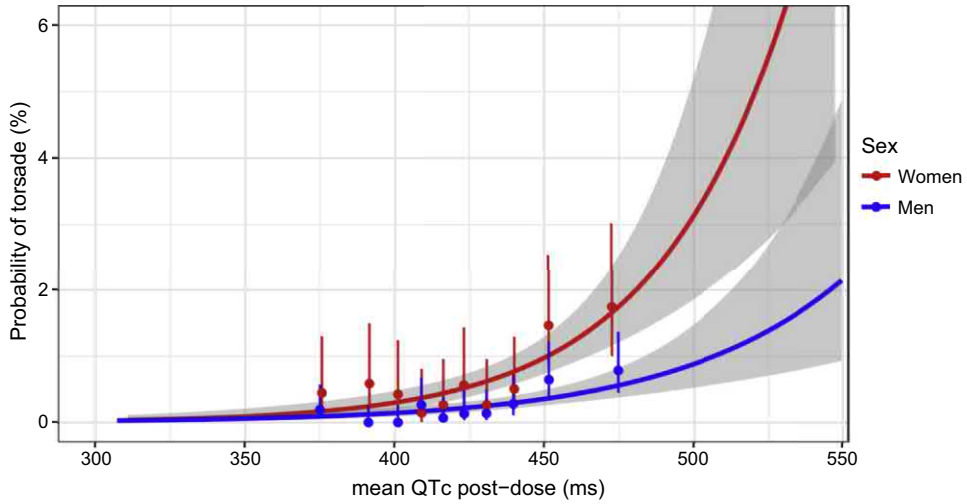

FIGURE 72.2 Relationship between heart rate corrected QT (QTc) postdose and torsade de pointes risk using logistic regression grouped by sex. Mean (*solid line*) and 95% confidence interval (*shade area*) for women (red) and men (blue). Mean (dots) and 95% CIs (error bars) show probability for torsade in the observed data divided into deciles based on mean QTc postdose. *Adapted from Johannesen L, Garnett C, Luo M, Targum S, Sorensen JS, Mehrotra N. Quantitative understanding of QTc prolongation and gender as risk factors for torsade de Pointes. Clin Pharmacol Ther 2018;103(2):304–9.*

plasma dofetilide concentrations after correction for weight and creatinine clearance [20]. Dosing based on body weight has been used to decrease variability in concentrations for some antiarrhythmic drugs, such as disopyramide, quinidine, and ibutilide. Despite body-weight dosing, prior studies showed women taking ibutilide [21] and quinidine [22] still have longer QTc intervals indicating that the pharmacokinetic differences may contribute but are unlikely to be a primary cause of sex differences in drug-induced QT prolongation. Results from these two studies are discussed in the "Increased Sensitivity to Drug-Induced QTc prolongation" section below.

Studies have reported physical, physiological, hormonal, molecular, and genetic differences between women and men affecting the drug exposure in systemic circulation and at the site of action [14]. A summary of various factors that can influence the pharmacokinetics of drugs are shown in Table 72.1 [14,17,23,24]. Interrelated and overlapping effects stemming from these factors can result in different drug exposures in women and men despite weight-adjusted dosing. For example, the differences in water retention and adipose tissues may result in increased volume of distribution of certain lipophilic drugs [25–27] translating into prolonged elimination half-life and tissue accumulation over time leading to adverse drug reactions, e.g., for diazepam [28,29], chlordiazepoxide [30], and olanzapine [31]. Conversely, the volume of distribution of hydrophilic drugs, such as muscle relaxants, is lower in women resulting in a higher initial plasma concentration [32]. Recent clinical studies have revealed that the hormonal fluctuations of estrogen, progesterone, follicle-stimulating hormone, and luteinizing hormone in women are the primary cause of sex differences in the pharmacokinetics of several drugs [33–35]. The plasma concentrations of sex hormones during reproductive life (e.g., premenopause, menstruation, pregnancy, and menopause) and use of oral contraceptives and hormonal replacement therapy can affect the drug disposition [17,35]. Regulatory guidelines have emphasized including both sexes in clinical trials such that the differences in drug effects between women and men are adequately characterized for the dose adjustment and described in product labels [36].

TABLE 72.1 Summary of the causal factors affecting the drug disposition processes.

Absorption:

- Gastrointestinal motility[a,c] (delayed in women)
- Intestinal enzymatic activity (lower in women)
- Gastric acid excretion and gastrin concentrations (lower in women)
- Bile–salt composition, pH, and buffer capacity [37]
- Minute ventilation (inhalation route; greater in women)
- Tidal volume (inhalation route; lower in women)
- Skin thickness (dermal route; lower in women)
- Skin hydration and blood flow[c] (dermal route)
- Cardiac output[c] (lower in women)
- Heart rate [higher in women [38,39]]

Distribution:

- Protein binding and binding capacity
  - Levels of albumin, lipoproteins, and alpha-1 acid glycoprotein[a] [lower in women [40]]
- Body weight, body composition, plasma volume[c,d] (lower in women)
- Proportion of body fat and adipose tissue [higher in women [35]]
- Body surface area[c] (lower in women)
- Muscle mass (lower in women)
- Organ size (smaller in women) and organ blood flow (higher in women)
- Transporters expression
  - Hepatic Pgp expression[a] [lower in women [41]]

Metabolism:

- Hepatic blood flow[c] [lower in women [42]]
  - Expression and hepatic activity of metabolizing enzymes [43]
  - Sex-specific expression of metabolic enzymes in phase-I metabolism
    - Expression of CYP3A4[a,d,b] (postmenopause vs. premenopause)
    - Expression of CYP1A2[b] (lower in women) [14]
    - Expression of CYP2C9 (lower in women)
    - Expression of CYP2D6 (lower in women)
    - CYP2B6 [44]
  - Sex-specific expression of metabolic enzymes in phase-II metabolism
    - Glucuronidation (lower in women)
    - Glycine conjugation

Elimination:

- Glomerular filtration rate (lower in women but proportional to weight)
- Muscle metabolism
- Transporters expression (lower organic cation transporter expression[a])
- Intracellular and extracellular fluid volume and electrolyte balance[d]
- Sex-specific differences in organs (liver, kidney, skin, lungs, etc.)

[a]Possibly regulated by sex hormones.
[b]Possibly impacted by growth hormone, proportional to body weight or body–surface area (GFR).
[c]Possibly altered during pregnancy.
[d]Possibly altered during menstrual cycle.

Longer baseline QTc intervals in women

The QTc interval at baseline is longer in women than in men. This sex difference in QTc is maintained throughout adulthood and gradually decreases with age more than 50 years [45]. In an analysis of data submitted to the Food and Drug Administration between 2001 and 2018, baseline QTc intervals corrected for heart rate using Fridericia's correction [46] (QTcF) were pooled from 15,682 women and

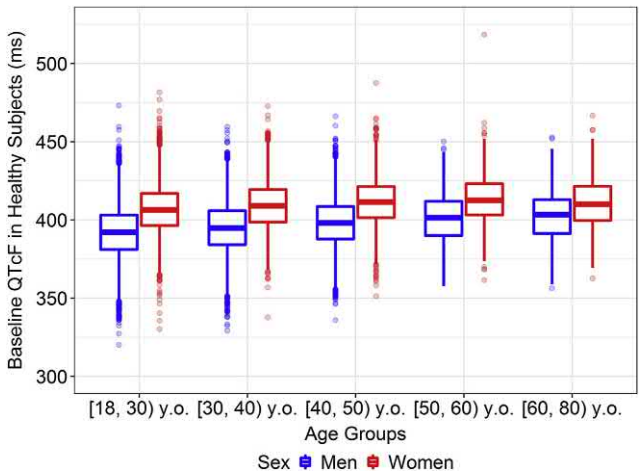

FIGURE 72.3 In thorough QT studies in healthy adult subjects, women (red) have longer baseline QTc compared to men (blue). Box plots show the median (*horizontal line*), 25th and 75th percentile (box); 1.5* interquartile range (whiskers); and outliers (circles).

22,288 men in 387 thorough QT (TQT) studies for comparison by age groups (Fig. 72.3). The mean baseline QTcF was consistently longer in women than in men younger than 60 years old by a mean of 12−15 ms across the age groups. In healthy subjects older than 60 years, the mean baseline QTc was 8 ms longer ($P < .001$) in women than in men; however, the distribution of values largely overlaps in the two populations. These results are in agreement with prior observations in a subset of 2235 healthy subjects (41% women) from TQT studies [47] and in a large database of epidemiological studies [48]. In exposure−response analyses of data from Phase 1 studies, female sex has been identified as a significant covariate that is associated with longer baseline QTc [49,50].

The sex difference in baseline QTc interval has been associated with endogenous sex hormones in different age groups. Testosterone is the primary sex hormone that regulates male traits. Throughout puberty and adulthood, testosterone concentration in men is 10-fold higher than that in women and it drops rapidly between the ages of 50 and 60 years [51]. Testosterone has been shown to shorten the cardiac action potential in nonclinical studies by blocking the L-type calcium (I_{CaL}) depolarizing current and enhancing the slow repolarizing delayed rectifier potassium current (I_{Ks}) [52,53] and to be inversely correlated with the QTc interval in clinical studies in men [54−56]. Estrogen and progesterone are the primary hormone that regulates female traits and functions. The estrogen concentration in women is approximately twice the concentration in men and decreases gradually after the age of 40 years [51]. Progesterone concentrations fluctuate during menstrual cycle. Like testosterone, progesterone has been shown to shorten action potential duration in in vitro patch clamp assays by reducing I_{CaL} and increasing I_{Ks} [57]. Consistent with the nonclinical findings, a small sample size clinical study in 11 healthy female subjects with regular menstrual cycles and 12 healthy men suggested that, in women, QTc intervals were longer in the follicular phase than in the luteal phase in which the serum progesterone concentration was significantly higher [58]. Estrogen has been shown to prolong action potential duration and QTc interval in mice and rabbits [59,60]. An analysis of estrogen concentrations and QTc interval in healthy, premenopausal women could be complicated due to fluctuation in serum concentrations and the counteracting effect of progesterone. Overall, endogenous testosterone and progesterone have been reported to shorten QTc interval in human while estrogen delay cardiac repolarization in nonclinical models [61].

The use of exogenous hormone therapy provides supporting evidence on the role of sex hormones on QTc interval. For example, statistically significant increase in mean QTc interval was observed in healthy postmenopausal women who were currently on estrogen-alone hormone therapy than in those who were never treated with menopausal hormone therapy or who were currently on combined estrogen−progesterone therapy [62]. Lastly, testosterone supplementation shortened QT and QTc interval in both male and female subgroups in a placebo-controlled study [63]. In addition to potentially shorten QTc, I_{CaL} block by testosterone and progesterone may play a protective role against TdP because I_{CaL} block has been shown to prevent the occurrence of early afterdepolarizations, the triggers of TdP, in in vitro assays [64,65].

Increased Sensitivity to drug-induced QTc prolongation

In addition to higher exposure and longer QT at baseline, another explaining factor for a higher drug-induced TdP risk in women could be that women are more sensitive to drugs that delay cardiac repolarization. Increased sensitivity means that drug concentrations and duration in the body would be similar in men and women, but women would respond to a greater extent. Some studies have suggested that women might be more sensitive to drug-induced QTc as evidenced by a steeper concentration−QTc relationship, which would further underscore the need for accounting for differences in postdose QTc. However, these findings were confounded by other factors, there were no systematic sex differences in the drug-induced response across drugs, and recent studies with large drug-induced QTc effects did not find sex differences in QTc slope of several antiarrhythmic drugs.

Benton and colleagues showed that women had a steeper quinidine concentration−QTc slope than men in a

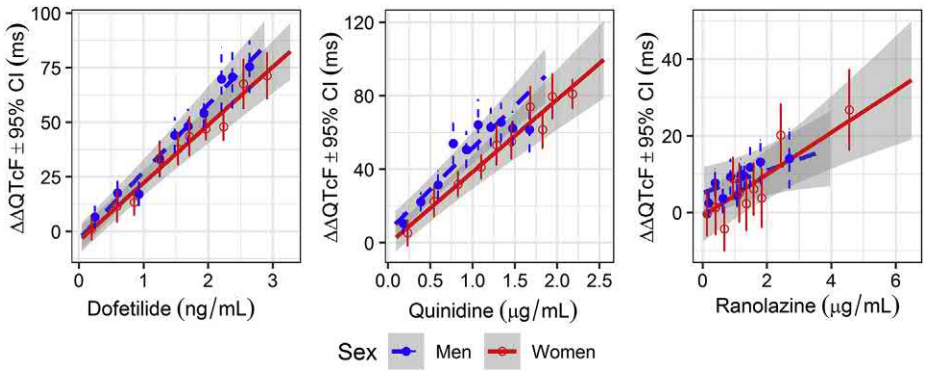

FIGURE 72.4 Sex-specific concentration–QTc models for dofetilide, quinidine, and ranolazine show no sex differences in the average exposure–response relationship (i.e., slope) of women (*red solid line*) versus men (*blue dashed line*). Shaded areas show the 95% confidence interval (CI) from the model predictions. Dots and error bars show mean and 95% CI of observed data binned in concentration deciles by sex group. *Data from Vicente J, Johannesen L, Mason JW, Pueyo E, Stockbridge N, Strauss DG. Sex differences in drug-induced changes in ventricular repolarization. J Electrocardiol 2015;48(6):1081–7.*

clinical study of intravenous quinidine [22]. However, this study was confounded by a delay between quinidine concentration and QTc changes (hysteresis) in men but not in women. A study of QTc effects caused by intravenous quinidine found similar sex difference in concentration–QTc response in Caucasians, but not in Korean healthy subjects [66]. Interestingly, there was no concentration–QTc hysteresis in this study, and a linear model was not sufficient to describe quinidine-induced QTc effects. In a study of a low-dose infusion of ibutilide, women had longer QTc prolongation than men [21]. While concentration–QTc analysis was not performed in the study, ibutilide concentrations were the same in women and men. In addition, this study showed that the baseline QTc did not change in women during the menstrual cycle, but the ibutilide-induced QTc prolongation was highest during menses and statistically significant less during the luteal phase. There was a negative correlation between progesterone and QTc changes in women, which suggested a potential protective role of sex hormones. The potential role of progesterone to mitigate ibutilide-induced QTc prolongation was assessed in another crossover study in 15 healthy women receiving an intravenous infusion of ibutilide, pretreatment and concomitant use of oral progesterone significantly shortened QTc before and after ibutilide administration [67]. Darpo and colleagues reported a steeper sotalol concentration–QTc slope in women following administration of a single oral dose of rac-sotalol [68]. The study used individualized QT/RR correction (QTcI) to account for the significant HR decrease caused by rac-sotalol (i.e., ~20 beats per minute around peak concentrations). However, it is possible that results may still be confounded in part by the large heart rate changes despite the QTcI correction [69,70].

There are other studies showing no sex differences in the drug concentration–QTc relationship. Vicente and colleagues performed a retrospective analysis and showed that there was a delay between quinidine concentration and QTc changes in men but not in women, and that there were no differences in quinidine concentration–QTc slopes after accounting for hysteresis in Benton's quinidine study discussed above [71]. This lack of sex differences in drug concentration–QTc slopes for quinidine is consistent with a recent prospective clinical study [72] that did not find sex differences in drug concentration–QTc slopes for dofetilide, quinidine, and ranolazine (Fig. 72.4). In addition, there were no systematic sex differences in concentration–response slopes for other ECG biomarkers, which included ECG subintervals and T-wave morphology measures. These findings were also consistent with no sex differences in dofetilide concentration–QTc slope in another prospective clinical study by Johannesen and colleagues (data not shown [73]). Lastly, a pooled analysis of moxifloxacin data from 20 TQT studies found women having longer placebo-corrected change from baseline QTc compared to men. However, these differences were explained by higher moxifloxacin concentrations in women, and no sex differences in moxifloxacin concentration–QTc slope were found [18]. Overall, these studies showed women are not more sensitive than men to the studied QTc prolonging drugs; that is, these results suggest that the higher TdP risk in women compared to men is not due to steeper concentration–QTc slopes.

Conclusion

Women have a higher rate of TdP when taking QT-prolonging medications that can be in part explained by their longer QTc intervals—women have longer QTc intervals at both baseline and on-treatment compared to men. In the FDA database, healthy women have an average of 12–15 ms longer baseline QTc intervals and the

differences in baseline values are less pronounced at ages above 60 years. Endogenous sex hormones may play a key role in the longer QTc at baseline where testosterone is thought to shorten the cardiac action potential by blocking the L-type calcium depolarizing current and enhance the slow repolarizing delayed rectifier potassium current. Pharmacokinetic differences can cause women to have higher plasma concentrations and longer retention in the body of QT-prolonging medications administered by fixed dose levels. Since most drugs prolong the QTc interval in a concentration-dependent manner, higher concentrations in women lead to higher drug-induced QTc prolongation. Women are not, however, more sensitive to the QTc prolonging effects of drugs—the slope of the concentration−QTc relationship for drugs is not systematically higher than men. Pharmacokinetic differences may contribute but are unlikely to be a primary cause of sex differences in drug-induced QT prolongation and increased risk of TdP. Women taking antiarrhythmic drugs have twofold the TdP risk after adjusting for on-treatment QTc values. This highlights the importance of identifying other physiological factors that may contribute to the increased TdP risk in women.

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Chapter 73

Acquired long QT syndrome and sex hormones

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Acquired long QT syndrome

The acquired long QT syndrome (acqLQTS) is a life-threatening condition, in which an acquired impairment of cardiac repolarization confers an increased risk for the development of polymorphic ventricular arrhythmias—especially torsade de pointes (TdP)—which may degenerate into ventricular fibrillation. Such arrhythmic events may be perceived by patients as tachycardiac palpitations, or they can lead—if sustained—to syncope or to sudden cardiac death [1,2].

AcqLQTS can be caused by a great variety of cardiac and noncardiac drugs, all impacting on cardiac repolarization phase (despite their differences in their mode of action or structure), and is often facilitated or accentuated by electrolyte imbalances, such as hypokalemia or hypomagnesemia [3].

Drugs (or metabolites) cause acqLQTS by interacting with cardiac repolarizing ion channels/currents. The most common mechanism involves an interaction with the KCNH2/HERG α-subunit of the potassium channel conducting the rapid delayed rectifier repolarizing potassium current I_{Kr} [4,5]. This current plays a crucial role in repolarizing phases 2 and 3 of the ventricular myocardial action potential. Thus, an alteration in the functionality of KCNH2/HERG, leading to a reduction or loss of I_{Kr} current, causes a prolongation of the action potential, clinically manifesting with a prolongation of the QT interval in surface ECG [6].

The reason for the preferential blockade of the HERG/I_{Kr} channel resides in the fact that KCNH2/HERG proteins have aromatic amino acids (Tyr652 and Phe656) with side chains directed toward the large central cavity of the pore region generating high-affinity binding sites for many compounds of various different structures [7]. These characteristics make the HERG/I_{Kr} channel a relatively "sticky channel." Besides this, in most of the other cardiac ion channels the access to the drug-binding site is restricted by two proline residues in the helix that forms part of the pore. The absence of such proline residues in KCNH2/HERG may contribute to its increased susceptibility to drug binding and inhibition [7].

Moreover, some drugs may inhibit the activity of I_{Kr} by interacting with the intracellular trafficking of KCNH2/HERG to the cell surface [8]. The responsible mechanisms include interactions with cytosolic chaperons as heat shock proteins Hsp70 and Hsp90, which has been reported for arsenic trioxide [9] or for the antibiotic drug geldanamycin [10]. Other drugs affect KCNH2/HERG by accelerating its degradation, as reported for the cholesterol-lowering drug probucol, which accelerates caveolin-1 turnover [11]. A reduction of I_{Kr} activity through interaction with KCNH2/HERG intracellular trafficking has been reported among others for cardiac glycosides [12], ketoconazole [13], and fluoxetine [14,15].

Beyond the inhibition of I_{Kr}, other pathophysiological mechanisms have been identified as possible causes of acqLQTS. The blockade of slow delayed rectifier potassium ion current I_{Ks}, for example by inhalative anesthesia, such as isoflurane, may cause QT prolongation and ventricular arrhythmias [16,17]. This effect is particularly enhanced in patients with reduced repolarization reserve or congenital LQTS, as previously demonstrated in transgenic LQTS rabbits [18]. Similarly, a blockade of the inward rectifier potassium current I_{K1}, as exerted, for example, by the widely used sedative midazolam, may cause a pronounced QT prolongation in individuals with reduced repolarization reserve or congenital LQTS [18].

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Other suggested mechanisms for the induction of acqLQTS and drug-induced arrhythmias include the enhancement of the late sodium current $I_{Na,L}$, as observed for dofetilide [4].

It is important to note that the individual's risk for developing TdP after the administration of known QT-prolonging drugs with proarrhythmic potential is highly variable. The risk is tightly related to the single individual's repolarization reserve, i.e., the extent of functional repolarizing ion currents in the cardiomyocyte [19]. Some patients show a significant prolongation of the QT interval after administration of potentially proarrhythmic drugs, whereas in other patients, the same dosage of the same drugs does not visibly alter the electrical properties of the cardiomyocytes. The susceptibility to acqLQTS can be seen, therefore, as a continuous spectrum, in which the single individual's extent of repolarization reserve may confer a very low up to a very high risk of QT prolongation and/or drug-induced TdP after administration of drugs interfering with cardiac electrophysiology. At the end of this spectrum are patients affected by congenital LQTS, in which QT prolongation and an increased risk for TdP and SCD are present even without any additional external stressors [20,21].

Sex differences in acquired long QT syndrome in human subjects

Sex differences in electrocardiographic features have been widely described in the past decades. As already identified by H.C. Bazett in 1920, healthy women show longer heart rate−corrected QT intervals (QTc) than men [22]. The sex difference in QTc duration is usually approximated to 20 ms [23], so that the upper limits for the "normal" QTc are set at 440 ms for men and 460 ms for women [2]. This sex difference becomes apparent with the onset of puberty and diminishes after menopause, indicating an impact of sex hormones on repolarization [24]. In addition, the QT/RR restitution curve is steeper in women than in men, implying a more pronounced sex-related QTc difference at slow heart rates [25,26]. Also, sex differences have been observed concerning the morphology of the T wave and, notably, regarding the QT dispersion, a marker of arrhythmic risk [27,28].

In addition to baseline sex differences in cardiac repolarization, pronounced differences can be observed in the extent of drug-induced QT prolongation. In female subjects, a higher susceptibility to drug-induced QT prolongation has been described for nearly all (potassium channel-blocking) class III antiarrhythmic drugs [29], such as amiodarone [30,31], ibutilide [32], dofetilide [33], and sotalol [29,34]—as well as for other antiarrhythmic drugs, such as quinidine [35,36], and for noncardiac drugs [37−39], such as erythromycin [40] or cisapride [41,42] (Table 73.1). Data from observational studies suggest that the overall occurrence of drug-induced TdP may be two to three times higher in women than in men [43−46]. Lehmann et al. observed a higher incidence of TdP in women than in men after administration of d,l-sotalol (4.1% of females vs. 1.9% of males) [34] (Fig. 73.1). De Bruin et al. reported that 68% of the adverse drug reaction reports of TdP concern female subjects [5]. Not only TdP but also drug-related sudden cardiac death occurs with a higher incidence in women than in men [47,48].

TABLE 73.1 Drugs associated with higher risk for drug-induced Torsade de Pointes in women than in men.

Reported incidences of drug-induced TdP		
Drug	**Male (%)**	**Female (%)**
Dofetilide[33]	1.8	5.7
Sotalol[29]	1.0	4.1
Ibutilide[32]	3.0	5.6
Drugs associated with a higher risk of Torsade de Pointes in women than in men		
Amiodarone[30,31]	Pentamidine[28]	
Chlorpromazine[28]	Pimozide[28]	
Erythromycin[40]	Procainamide[43]	
Halofantrine[37]	Quinidine[36]	
Haloperidol[38]	Terfenadine[28]	
Methadone[39]	Thioridazine[38]	

Data derived from Refs. [28−33,36−40,43].

These sex differences observed in the clinical setting have several different causes: Firstly, sex hormones influence both baseline QT duration and repolarization reserve, which is responsible for the susceptibility to (further) drug-induced QT prolongation—through both genomic and nongenomic effects on cardiac ion channels [47]. Secondly, sex differences in pharmacokinetics lead to relevant differences in the drug serum levels, since the dosage of substances is usually only adapted to the body surface area and/or to the body weight but not to the sex [40].

Sex hormone effects on QT prolongation and arrhythmogenicity in human acquired long QT syndrome

To date, the biological causes underlying sex differences in the risk for drug-induced acqLQTS and drug-induced TdP are not yet completely understood. It is apparent, however,

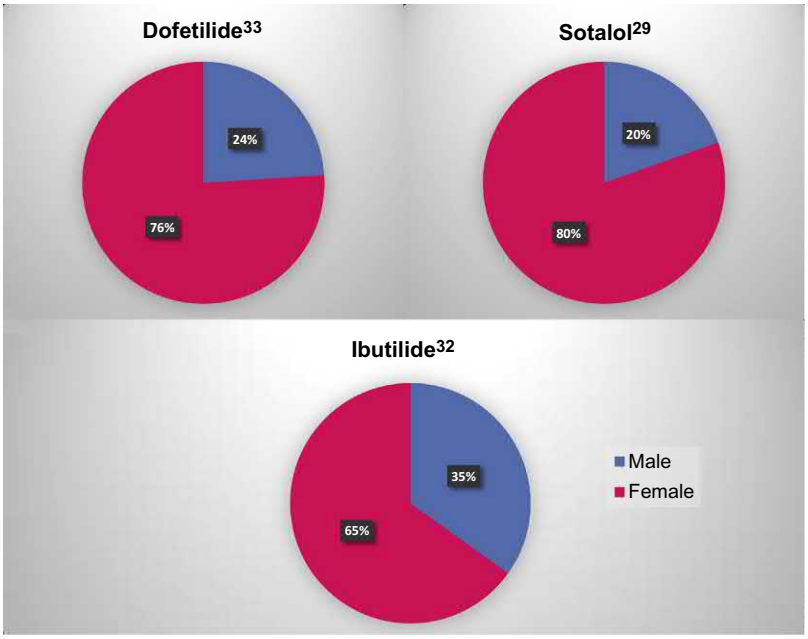


FIGURE 73.1 Portion of males and females (in %) among all patients presenting with Torsade de Pointes arrhythmias during therapy with dofetilide, sotalol, or ibutilide. *Data derived from Wolbrette DL. Risk of proarrhythmia with class III antiarrhythmic agents: sex-based differences and other issues. Am J Cardiol 2003;91:39–44; Gowda RM, Khan IA, Punukollu G, Vasavada BC, Sacchi TJ, Wilbur SL. Female preponderance in ibutilide-induced torsade de pointes. Int J Cardiol 2004;95:219–222; Torp-Pedersen C, Møller M, Bloch-Thomsen PE, Køber L, Sandøe E, Egstrup K, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. N Engl J Med 1999;341:857–865.*

that sex hormones have a pronounced influence on cardiac ion channels/currents and repolarization reserve by affecting transcription, expression, and functionality of cardiac ion channels, predisposing adult women to a higher risk of acqLQTS and drug-induced TdP than men [49,50].

Estradiol and testosterone seem to play the main roles in determining sex differences in (acq) long QT-related arrhythmic risk: Estradiol increases the arrhythmic risk, and testosterone exerts a beneficial protective effect [47]. For a more thorough understanding of sex differences in this arrhythmic risk, the effects of progesterone [51], FSH [52], and the postpartum-associated hormones oxytocin and prolactin [53] should also be considered.

In human cardiac tissue (right and left ventricles) derived from nondiseased transplant donors, the transcript and protein expression of several repolarizing K^+-channel subunits—such as KCNH2/HERG, KCNE1, and Kir2.3—was demonstrated to be reduced in female hearts, compared with analogous male tissue [54]. These results of Gaborit et al. [54] indicate pronounced similarities between the sex differences of cardiac ion channels observed in human hearts and the observations made in rabbits [55] and guinea pigs [56], according to which I_{Kr} and I_{K1} are smaller in female subjects than in males. In addition, the increase in the arrhythmic risk that accompanies the women's typical steeper QT-RR restitution curve may be due to an increased activity of cardiac Na^+/K^+ ATPase in women, which shortens the duration of cardiac repolarization, particularly at fast heart rates [57].

Finally, sex hormones may affect the activity of myocardial ion channels not only via changes in transcription and protein expression but also through a modulation of their posttranslational phosphorylation and through nongenomic effects on their activity involving nitric oxide [58]. All these mechanisms are elucidated in more detail in Mechanisms of sex hormone effects in acquired LQTS—insights from animal models section.

Sex differences in acquired long QT syndrome before and after puberty

Changes in cardiac repolarization characteristics and arrhythmic risk profiles throughout life—from infancy through early adult life to postmenopausal stages—provide strong clinical indications that sex hormones may play an important role in the modulation of myocardial repolarization [59] (Table 73.2).

At birth, no sex-related differences are observed in heart rate–corrected QTc, whereas the RR interval and the absolute QT duration are slightly, however, significantly shorter in female subjects [26]. Independent studies demonstrated that male prepubertal children with

TABLE 73.2 Sex hormones' influence on acqLQTS.

Sex hormones' influence on AcqLQTS – Schematic summary		Drug-induced QT prolongation	Drug-induced ventricular arrhythmias
Life phase	Childhood	♂ > ♀	♂ > ♀
	Adolescence and adulthood	♂ < ♀	♂ < ♀
Different hormonal phases in women	Follicular phase	- /↑	- /↑
	Luteal phase	- /↓	- /↓
	Postpartum	- /↑	↑
	Menopause	-	- /↑
Sex hormones	Estrogens	↑↑	↑↑
	Progesterone	↓	↓
	Testosterone	↓↓	↓↓
Hormone and anti-hormone therapies	SERMs	- /↑	↑
	AR-Antagonists	- /↑	↑
	OC – 1st/2nd generation	↓	↓
	OC – 3rd generation	-	-
	OC – 4th generation	- /↑	↑
	HRT – estrogen-based	↑	↑
	HRT – estrogen+progesterone-based	-	-

–, no change; ≤, lower than; ≥, higher than; ↑, increased; ↓, reduced; ♀, female sex; ♂, male sex; acqLQTS, acquired long QT syndrome; AR, androgen receptor; HRT, hormone replacement therapy; OC, oral contraceptive; SERMs, selective estrogen receptor modulators.

congenital LQTS have a higher risk of developing sustained ventricular arrhythmias and sudden cardiac death than female children in the same age [49,60] Similarly, in prepubertal age, QT-prolonging drugs cause a more pronounced QT prolongation and more early afterdepolarizations (EADs) and ventricular tachycardias in male than in female children [61].

The hormonal rearrangement during puberty brings about a reversal of sex differences in the arrhythmic risk pattern. Thus, in congenital LQTS, women aged 18–40 years show a 2.7 times higher arrhythmic risk that men of the same age [48]. Similarly, various independent studies report that drug-induced adverse arrhythmias occur in 66%–71% of the cases in women, instead of the expected 50% [43,62,63]. At puberty, the increment of testosterone serum level causes a shortening of the QTc in boys (both in healthy ones as in boys affected by LQTS) [64,65], whereas on the other side, estradiol peaks in girls, prolonging the QTc and conferring a higher arrhythmic risk in girls and women [48,66] (Table 73.2).

Effects of menstrual cycle, pregnancy, and postpartum on acquired long QT syndrome

In adult women, hormone levels vary pronouncedly during different phases of the menstrual cycle, pregnancy, and the postpartum [48]. As a consequence, different phases of the menstrual cycle and pregnancy, as well as the postpartum period, are all associated with changes in baseline QTc duration, the extent of drug-induced QT prolongation, and the incidence of (drug-induced) polymorphic ventricular tachycardias [67,68].

The physiological progressive increase of estradiol during the follicular phase and the predominance of progesterone during the luteal phase influences repolarization reserve and the duration of cardiac repolarization in healthy subjects as well as in congenital and in acqLQTS [69–71]. Several studies reported longer QTc in the follicular phase than in the luteal phase, suggesting a QT-prolonging effect of estradiol and a QT-shortening effect of progesterone [44,72], whereas others report that without "external

stressors." QTc and QT-RR restitution curve do not undergo relevant changes during the menstrual cycle [72–74]. Various studies have been conducted to assess changes in the arrhythmic risk during the menstrual cycle—also reporting partially conflicting data [75]. The most consistent evidence suggests that the estradiol concentration positively correlates with the risk for drug-induced acquired QT prolongation and drug-induced ventricular tachycardias [67], reaching the top in the preovulatory phase and the bottom in the early follicular phase [76] (Table 73.2).

No study examined thoroughly the risk of acquired long QT syndrome, and drug-related arrhythmic events during pregnancy and the available data in congenital LQTS are contrasting [70,71]. While Seth et al. did not observe any QTc changes during pregnancy and reported a reduced incidence of arrhythmic events in congenital LQTS [68], we and others observed a shortening of the QTc during pregnancy [70,71].

Hemodynamic changes, cardiac remodeling [77], alterations in adrenergic activity [78], disrupted sleep pattern [79], and hormonal changes [53] all contribute to the increased arrhythmic risk in the postpartum phase in congenital LQTS [68]. Data on potential changes in the risk for acqLQTS during the postpartum phase, however, are not available to date.

Effects of menopause and hormone replacement therapy on acquired long QT syndrome

In adult women, pronounced hormonal changes occur during and after the menopausal transition, e.g., a pronounced reduction of estradiol levels and an increase in FSH [80]. Studies comparing ECGs in pre- and postmenopausal women did not detect any differences in QT or QTc intervals [81]. The observation of an increased QT dispersion in postmenopause, reported by Saba et al. however, suggests that postmenopausal women may be at high arrhythmic risk due to a reduction of the repolarization reserve [82]. Indeed, despite the lack of high estradiol levels, postmenopausal women remain at higher risk for arrhythmias than men of the same age in congenital LQTS—and in multivariate model predictions [46,83]. Solid clinical data demonstrating a higher susceptibility for acqLQTS and drug adverse arrhythmic reactions in postmenopausal women, however, are still missing.

Many studies have inquired the impact of (postmenopausal) hormone replacement therapy (HRT) on myocardial repolarization. Initial reports were contrasting: some authors observed a reduction in QT dispersion in women receiving HRT [84], whereas other studies reported no changes in QT dispersion or QTc intervals [85,86] or even an increase of QT dispersion and QTc intervals [87]. Insights into a potential explanation of the discrepancies were provided by Carnethon et al. who observed that women on estrogen-only HRT had an increased incidence of QTc prolongation compared with women without HRT [88]. In contrast, estrogen–progesterone-based HRT was not associated with a change in the QTc, suggesting a counterbalancing effect of exogenous oral estrogen and progesterone (Table 73.2).

Effects of oral contraceptives on acquired long QT syndrome

The protective role of progesterone was also supported by studies on the effects of oral contraceptives (OCs) on QT interval. The available OC therapies are classified into four generations according to the progestin-type they contain in addition to the estrogens: First- and second-generation OC therapies contain androgenic progestins; third-generation OCs have less androgenic progestins; and fourth-generation progestins are nontestosterone derived and antiandrogenic [89]. Comparative analyses of the different OC generations in regard to their effect on the cardiac electrophysiology indicated that first- and second-generation OCs shortened the QT interval, whereas the third-generation OC did not affect QT duration and fourth-generation OC prolonged slightly but significantly the QTc (+4 ms) [89] (Table 73.2).

Effects of abnormal hormone levels and antihormonal therapy on acquired long QT syndrome

Pathological conditions affecting the hormonal status also influence the myocardial repolarization. Women with abnormally elevated androgens concentrations have shorter QT intervals even despite higher estrogens serum levels [86]. Conversely, in castrated men and in men undergoing androgen deprivation therapies, the cardiac action potentials/QT intervals are longer and get shortened after testosterone substitution therapy [64,90]. In addition to QT prolongation by androgen deprivation therapies, various studies report also a higher incidence of drug-induced adverse arrhythmic reaction in such patients [91,92].

Another frequent alteration of the sex hormone status is caused by treatment with selective estrogen receptor modulators (SERMs). Tamoxifen, one of the most used SERMs [93], and toremifene seem to exert a relatively mild QT-prolonging effect [94] but increase the risk of TdP and

sudden cardiac death [95,96]. Studies in animal models and human embryonic kidney cells demonstrated that tamoxifen and its active metabolite, endoxifen, prolong the myocardial action potential through a concentration-dependent inhibition of I_{Kr} [97–99]. The I_{Kr} inhibition takes place through a double mechanism, which involves a direct channel blockage and the disruption of channel trafficking to the plasma membrane [100]. In addition to I_{Kr} inhibition, tamoxifen inhibits sodium [98] and L-type calcium currents [101]. It is reasonable to assume that patients undergoing a treatment with SERMs may be affected by a significant reduction of the repolarization reserve, only partially reflected in the QT prolongation, which exposes the subject to a higher risk of drug induced arrhythmic events (Table 73.2).

Mechanisms of sex hormone effects in acquired LQTS—insights from animal models

Different animal models have been used to investigate sex hormone effects on myocardial repolarization and the propensity to drug-induced long QT-associated arrhythmogenesis. In addition to mice—which represent the most widely used animal models for cardiovascular research [102] despite pronounced differences in myocardial repolarization and its main contributing ion currents compared with human physiology—many data on the cardiac electrophysiology were collected from studies with guinea pigs and rabbits. That is because guinea pigs' and rabbits' repolarizing ion currents more closely resemble human currents [103–107]. Additionally, rabbit models mimic human sex differences in cardiac repolarization and in (acquired and genetic) LQT-related arrhythmias [47,55,75,108].

Like human subjects, female rabbits have longer QT intervals [55] than males, as well as a steeper QT/RR slope [18], a higher transmural APD dispersion [109], and a more pronounced QT prolongation after administration of I_{Kr}-blocking drugs [110]. Besides this, female rabbits show a higher incidence of drug-induced ventricular tachycardias than males [108]. These sex differences in QT duration and in the risk for drug-induced arrhythmias can be mimicked by testosterone and estrogen (Figs. 73.2 and 73.3) [51,111,112].

The advances offered by such animal studies are their potential to gather insights into the cellular/molecular mechanisms by which the different sex hormones influence the expression and function of various cardiac ion currents.

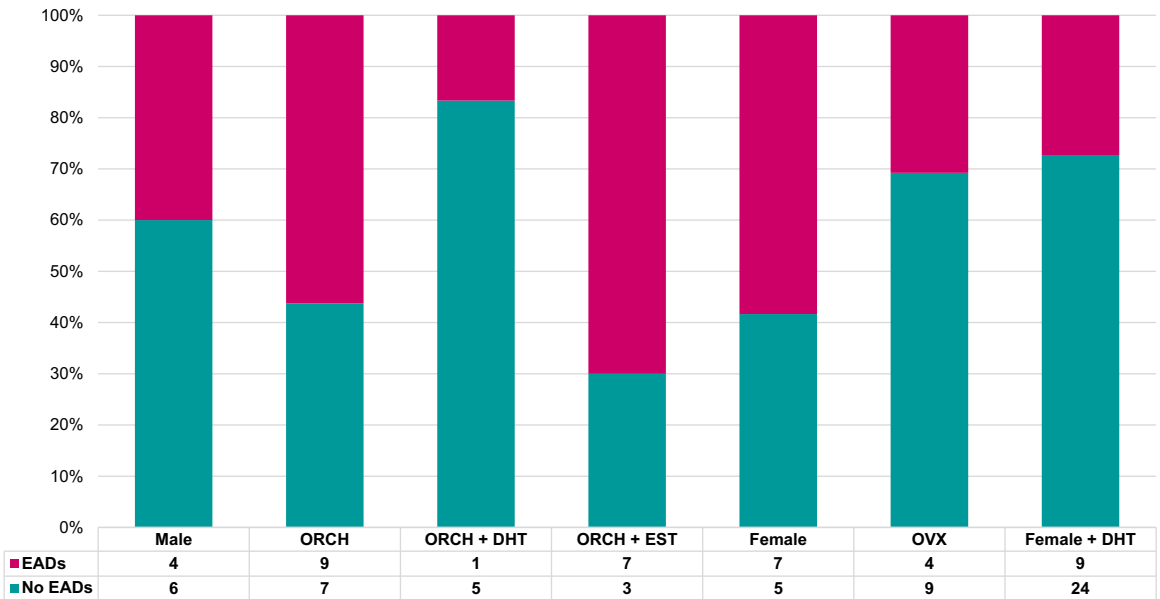
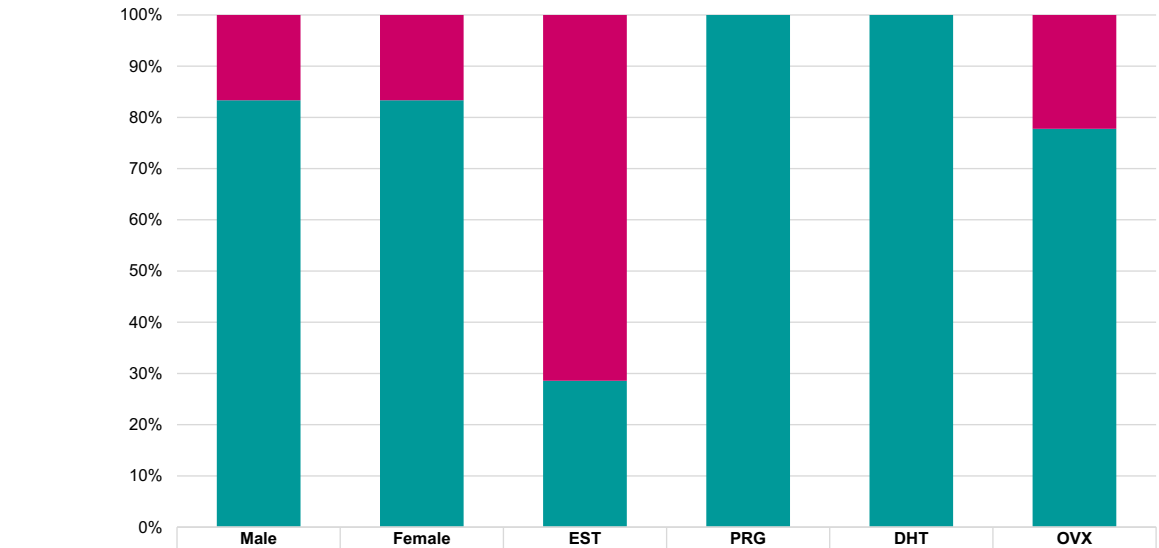


FIGURE 73.2 Sex hormones and incidence of drug-induced early after depolarization (EAD) in wild-type rabbit models. Incidence of EADs after administration of 10^{-6} mol/L dofetilide in control male and female rabbits, in control orchiectomized (ORCH) male rabbits, in orchiectomized male rabbits after administration of estrogen (ORCH + EST) or testosterone (ORCH + DHT), in oophorectomized female rabbits (OVX), and in female rabbits after administration of testosterone (Female + DHT). *Data derived from Pham TV, Sosunov EA, Anyukhovsky EP, Danilo P, Rosen MR. Testosterone diminishes the proarrhythmic effects of dofetilide in normal female rabbits. Circulation 2002;106:2132–2136; Pham TV, Sosunov EA, Gainullin RZ, Danilo P, Rosen MR. Impact of sex and gonadal steroids on prolongation of ventricular repolarization and arrhythmias induced by IKr-blocking drugs. Circulation 2001;103:2207–2212.*



	Male	Female	EST	PRG	DHT	OVX
Ventr. Arrhythmias	1	1	5	0	0	2
No Arrhythmias	5	5	2	9	9	7

FIGURE 73.3 Sex hormones and incidence of arrhythmias in transgenic LQT2 rabbits. Incidence of spontaneous ventricular arrhythmias (non-sustained and sustained ventricular tachycardias and sudden cardiac death) during 2 h of telemetric ECG in transgenic LQT2 rabbits with chronic estrogen (EST), progesterone (PRG), or testosterone (DHT) exposure (hormone-releasing pellets) in comparison with control male, female, and oophorectomized female (OVX) LQT2 rabbits. *Data derived from Odening KE, Choi BR, Liu GX, Hartmann K, Ziv O, Chaves L, et al. Estradiol promotes sudden cardiac death in transgenic long QT type 2 rabbits while progesterone is protective. Heart Rhythm 2012;9:823–832.*

Estrogen

Estrogen affects cardiac action potential duration and the associated long QT-related arrhythmogenesis through numerous different mechanisms. Several studies have shown that 17β-estradiol can inhibit the inward rectifier potassium current (I_{K1}) and the delayed and rapid rectifier potassium currents I_{Ks} and I_{Kr} [113–115]. Estradiol inhibits I_{Kr} both directly by blocking the KCNH2/HERG channel and indirectly by increasing the transcription of the β-subunit KCNE2 [116]. Thereby, estradiol exerts a synergistic effect when combined with I_{Kr}-blocking drugs [117]. Similarly, the inhibition of I_{Ks} by estradiol is caused by a downregulation of the mRNA levels of KCNE1, the β-subunit to the ion channel conducting I_{Ks} [35].

Beyond the potassium currents, estradiol affects the regional expression and function of the L-type calcium channel ($I_{Ca,L}$) and the sodium–calcium exchanger (NCX). Studies in rabbits revealed a higher density of $I_{Ca,L}$ and I_{NCX} in cardiomyocytes from the ventricular base than from the apex in female—but not in male—hearts, thus enhancing a proarrhythmic dispersion of repolarization. This regional difference could be reproduced by incubation of isolated ventricular cardiomyocytes from female hearts with estrogen: Here, an estrogen-induced upregulation of mRNA, proteins, and current densities was observed in basal but not in apical cardiomyocytes [118,119]. The increase of $I_{Ca,L}$ was mediated by a genomic mechanism, e.g., an estrogen receptor binding to the promoter region of the gene encoding for the L-type Ca^{2+} channel [119]. By increasing $I_{Ca,L}$, estradiol enhances the propensity to develop EADs [51]. In summary, estradiol prolongs cardiac repolarization (particularly at slow heart rates) and increases the likelihood of drug-induced arrhythmias, exerting a proarrhythmic synergic effect with concomitant QT-prolonging drugs (Figs. 73.4 and 73.5).

Progesterone

In women, the estradiol-induced propensity to develop arrhythmias is partly counterbalanced by progesterone. Progesterone increases I_{Ks} current densities in a dose-dependent manner via a nongenomic pathway involving NO, thereby shortening the QT [58,120,121]. Secondly, both the acute and the chronic administrations of progesterone decrease $I_{Ca,L}$ current densities, antagonizing the aforementioned estrogen-mediated upregulation of $I_{Ca,L}$ [51,122].

Finally, studies in rats and rabbits showed that progesterone increases the expression and activity of the sarcoplasmic reticulum calcium ATPase SERCA [123]. The following increased Ca^{2+} reuptake into the sarcoplasmic reticulum, and shortening of Ca^{2+} transient duration may contribute to progesterone's antiarrhythmic effect [51]. These observations from experimental studies in animal

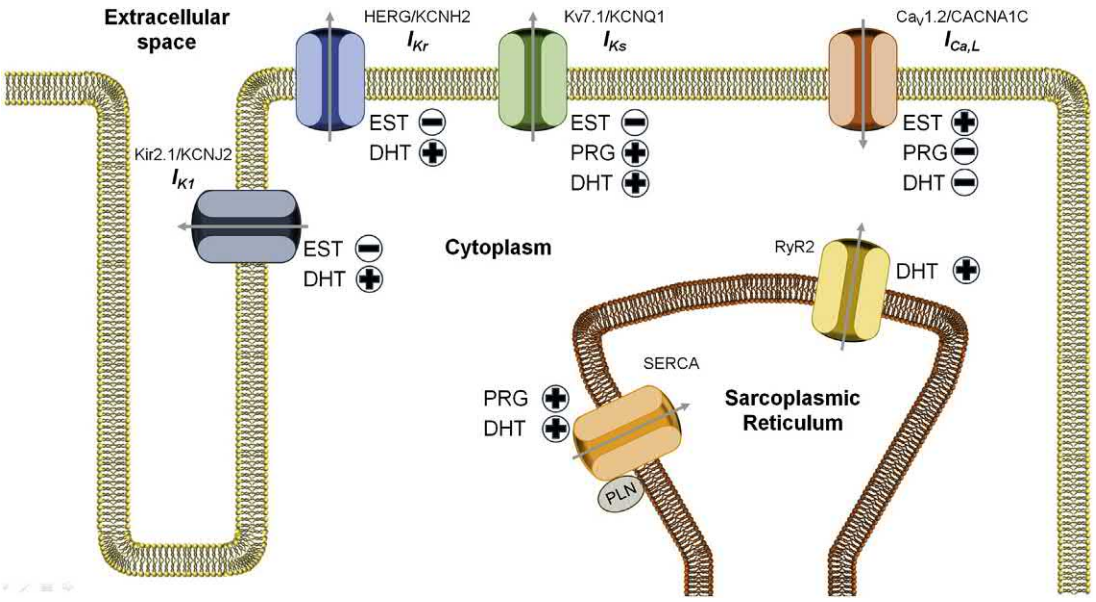


FIGURE 73.4 **Sex hormone effects on cardiac ion channels.** −, decrease; +, increase; *$Ca_V1.2$/CACNA1C*, α-subunit of L-type calcium channels conducting $I_{Ca,L}$; *DHT*, testosterone; *EST*, estradiol; *HERG/KCNH2*, channel conducting the rapid delayed rectifier repolarizing potassium current I_{Kr}; *Kir2.1/KCNJ2*, channel conducting the inward rectifier potassium current I_{K1}; *Kv7.1/KCNQ1*, channel conducting the slow delayed rectifier repolarizing potassium current I_{Ks}; *PROG*, progesterone; *RyR2*, ryanodine receptor 2; *SERCA*, sarcoplasmic reticulum calcium ATPase.

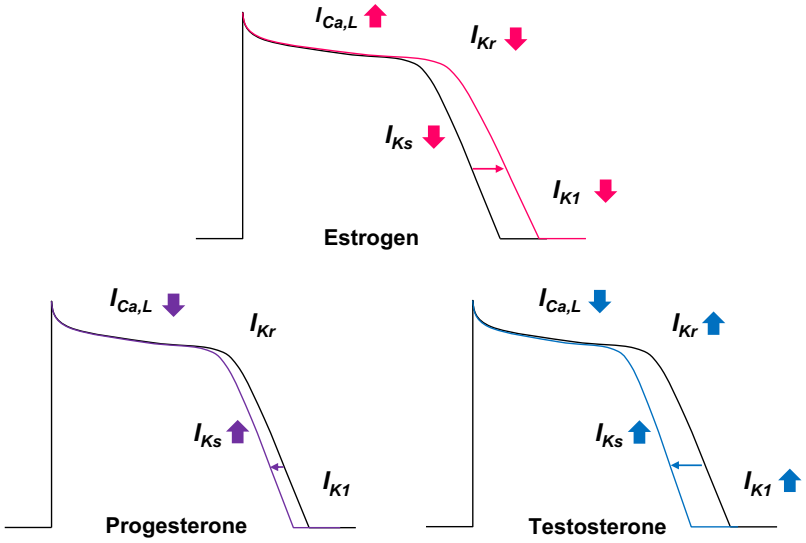


FIGURE 73.5 **Sex hormone effects on ion currents and action potential duration.** ↑, increase; I_{Kr}, rapid delayed rectifier repolarizing potassium current; ↓, decrease; *DHT;EST*, estradiol; $I_{Ca,L}$, L-type calcium current; I_{K1}, inward rectifier potassium current. Estrogen prolongs the ventricular action potential duration by inhibiting the repolarizing potassium currents I_{Kr}, I_K, and I_{K1} and by enhancing the depolarizing $I_{Ca,L}$ calcium current. Testosterone exerts opposite effects on the mentioned ion currents, causing a shortening of the myocardial action potential duration. A slighter shortening effect on the ventricular action potential duration is caused by progesterone, which inhibits $I_{Ca,L}$ and enhances I_{Ks}.; I_{Ks}, slow delayed rectifier repolarizing potassium current; *PROG*, progesterone; testosterone.

models are supported in a recent study in human subjects by Tisdale et al. [124]. Here, the investigators reported that the daily oral administration of 400 mg progesterone for 1 week significantly shortened QTc intervals during the follicular phase in young healthy women. In addition, the authors observed an attenuation of an ibutilide-induced QTc prolongation after progesterone administration [124].

In brief, progesterone shortens cardiac repolarization, attenuates QT-prolonging drug effects, and decreases the likelihood of drug-induced arrhythmias (Figs. 73.4 and 73.5).

Testosterone

Testosterone is another main actor in the determination of sex differences in cardiac repolarization and drug-induced arrhythmogenesis. Acute and chronic testosterone effects on cardiac action potential duration are partially opposing. An acute exposure to testosterone increases I_{Kr} and I_{K1}, resulting in an APD shortening [125,126]. Moreover, the administration of testosterone in physiological low concentrations was reported to acutely enhance I_{Ks} [110] via a nongenomic pathway involving NO [58]. Besides this, Masuda et al. observed an upregulation of Kv7.1 (KCNQ1) mRNA expression in cardiomyocytes of male and female rats after a 48-h exposure to testosterone [127], which may further increase I_{Ks} current densities.

Testosterone acutely inhibits $I_{Ca,L}$ [122], although contrasting effects may be observed after chronic exposure: Chronic testosterone administration has been reported to increase L-type calcium channel (Cav2.1) expression and $I_{Ca,L}$ densities [122,128]. Testosterone also enhances SERCA's function, leading to a faster removal of Ca^{2+} from the cytosol and shortened Ca^{2+} transient duration [129]. Additionally, testosterone increases the activity of the ryanodine receptor RyR2, which may lead to a faster inactivation of $I_{Ca,L}$ [129]. Finally, testosterone may increase NCX transcription and activity, as reported in a study on rat experimental models [130].

Electrocardiographic studies conducted in LQT2 rabbit models demonstrated a dihydrotestosterone-induced decrease in QT-RR curve slope steepness in female rabbit models, thus mimicking the male phenotype [51]. These data support the observational studies conducted by Van Noord et al. and by Zhan et al. which indicated that increasing levels of endogenous testosterone correlate with shorter QT intervals in adult men [24,131].

In summary, testosterone exerts a beneficial QT-shortening effect by shortening cardiac repolarization, attenuating the effects of QT-prolonging drug, and thus reducing the probability of drug-induced arrhythmia (Figs. 73.4 and 73.5).

Clinical implications

The aforementioned effects of sex hormones on myocardial electrophysiology help explain the clinically observed sex differences in the extent of QT prolongation and arrhythmic risk both for drug-induced, acquired, and congenital LQTS.

Adult women are per se at higher risk of drug-induced QT prolongation and drug-induced ventricular arrhythmias than men, and a special caution as well as a closer monitoring under QT-prolonging medication is advised in the postpartum and in the postmenopausal phases [68,82]. In these phases, observed changes in sex hormones and also in the autonomic tone may play an important role in triggering arrhythmic events [68], so that the administration of a β-blocker therapy (e.g., Nadolol or Propranol [132]) could prove to be particularly effective [68].

A complete patient clinical history should always include a considerate pharmacological medical history—including the explicit question regarding the potential use of hormonal preparations. Fourth-generation oral contraceptives seem to reduce the repolarization reserve, thus leading to an increased risk for drug-induced arrhythmia; on the contrary, first- and second-generation oral contraceptives may exert a protective antiarrhythmic effect due to the use of androgenic progestins [89]. Special caution and vigilance are required in patients under SERM or androgen receptor antagonist therapies, since both may increase the drug-induced arrhythmic risk—in case of SERM therapy by inhibition of multiple cardiac channels; in case of androgen receptor antagonist therapy by antagonizing the beneficial effects of testosterone [95,98,120].

A better understanding of the exact mechanisms underlying sex differences and sex hormone effects on cardiac electrophysiology may help better discern and minimize the individual risk for patients requiring treatments with QT-prolonging drugs.

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Chapter 74

Management of arrhythmias in pregnancy

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Arrhythmias

Tachyarrhythmias become more frequent and may even manifest for the first time during pregnancy. Atrial fibrillation (AF) and paroxysmal supraventricular tachycardia (SVT) are, apart from premature beats, the most frequent arrhythmias [1,2]. Even though symptomatic exacerbation of paroxysmal SVT occurs during pregnancy in 20%−44% of cases [3], most are benign and can be treated effectively with standard medical therapy.

New onset of ventricular tachycardia (VT) should be investigated for the presence of underlying structural heart disease and inherited arrhythmogenic disorders, since especially VT is associated with increased mortality risk [3].

Although the management of arrhythmias in pregnant women is similar to that of a nonpregnant patient, the hemodynamic effects of tachycardias and the side effects of treatments must be balanced and addressed for the well-being of the fetus, as well as for delivery and lactation [4]. Patients with a known history of any symptomatic tachyarrhythmia should therefore be considered for catheter ablation prior to pregnancy [5].

Management of arrhythmias

Antiarrhythmic drugs

Treatment of arrhythmias should be reserved for those causing hemodynamic compromise or significant symptoms. The major concern regarding the use of antiarrhythmic drugs during pregnancy is their potential adverse effects on the fetus. While the first trimester is associated with the greatest teratogenic risk, drug exposure later in pregnancy may confer adverse effects on fetal growth and development, uterine contractility, as well as increased risk of proarrhythmia [4]. The risk and benefit of continuing versus stopping medication must be carefully considered related to the risk of recurring tachyarrhythmia and their potential for hemodynamic compromise [4]. The decisions should be individualized based on the nature of the arrhythmia and the underlying heart disease. Major controlled studies of antiarrhythmic drugs during pregnancy are lacking. Antiarrhythmic drugs are listed in Tables 74.1 and 74.2.

Electric cardioversion

Electrical cardioversion should be the first choice when tachyarrhythmias are hemodynamically unstable. Cardioversion seems safe in all phases of pregnancy as it does not compromise blood flow to the fetus [6,7] and the risk of inducing fetal arrhythmias or initiating preterm labor seem small [8].

Catheter ablation

Catheter ablation may be necessary in the case of drug-refractory and poorly tolerated tachycardias but should be postponed to the second trimester if possible and performed at an experienced center using nonfluoroscopic catheter navigation and electroanatomic mapping systems [9,10]. Catheter ablation of recurrent drug-refractory SVT or certain VT may be considered as an alternative to avoid potentially harmful medications in pregnant patients [5].

Implantable cardioverter defibrillator

The presence of an implantable cardioverter defibrillator (ICD) does not itself contraindicate future pregnancy. Treatment with an ICD should be considered not only prior pregnancy in patients with high-risk factors for sudden cardiac death but also during pregnancy to protect

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TABLE 74.1 Recommendations for the management of arrhythmias in pregnancy.

Management of tachycardia
Immediate electrical CV is recommended for any tachycardia with hemodynamic instability.
Acute management of SVT
Acute conversion of PSVT—recommended drugs in order of preference: 1. Vagal maneuver followed by i.v. adenosine 2. I.V. beta-1 selective blocker (except atenolol) for conversion or rate control 3. I.V. digoxin for rate control if β-blockers fail 4. I.V. ibutilide for conversion of atrial flutter
Acute management of sustained VT
Acute conversion of VT—recommended therapy in order of preference: 1. Immediate electrical CV if sustained, unstable, or stable VT 2. I.V. sotalol[b] or procainamide for hemodynamically stable, monomorphic, and sustained VT 3. I.V. Amiodarone[b] for hemodynamically unstable, monomorphic, and sustained VT refractory to electrical CV or other drugs
Long-term management for prevention of SVT
SVT *without* preexcitation on resting ECG: 1. Oral beta-1 selective blocker (except atenolol)[a,c] or verapamil 2. Oral flecainide[d] or propafenone[d] if AV nodal–blocking agents fail
SVT *with* WPW syndrome: oral flecainide[d] or propafenone[d]
For rate control of AT/AF: oral verapamil[c] or digoxin[c] if beta-1 selective blocker fails
For prevention of AT/AF: Flecainide[d] or propafenone[d] if AV nodal–blocking agents fail to prevent AF
Dronedarone, amiodarone, and atenolol[a]is not recommended
Long-term management of sustained VT
β-Blocking agents for congenital long QT syndrome and CPVT
Idiopathic sustained VT: recommended drugs in order of preference 1. Oral metoprolol[a,c], propranolol,[a,c] or verapamil[d,c] 2. Oral sotalol[b], flecainide[d] if above drugs fail

For drug dosing information - refer to published guidelines on the management of patients with atrial fibrillation, supraventricular arrhythmias, and ventricular arrhythmias [4,5,18]. *AV*, atrioventricular; *CPVT*, catecholaminergic polymorphic ventricular tachycardia; *CV*, cardioversion; *ECG*, electrocardiogram; *i.v.*, intravenously, *SVT*, supraventricular tachycardia, *VT*, ventricular tachycardia.
[a]*β-Blocking agents should be used with caution in the first trimester.*
[b]*Class III drugs should not be used in cases with prolonged QTc.*
[c]*AV nodal–blocking agents should not be used in patients with preexcitation on resting ECG.*
[d]*Consider AV nodal–blocking agents in conjunction with flecainide and propafenone for certain atrial tachycardias.*

the mother's life as pregnancy does not cause an increased risk of major ICD-related complications [11,12]. Echocardiographic guidance or electroanatomical mapping may be helpful [13].

Antiarrhythmic drugs for supraventricular tachyarrhythmias

AV nodal reentry tachycardia or AV reentry tachycardia involving an accessory pathway should be terminated by vagal maneuvers as first-line treatment or, if that fails, by intravenous adenosine [14]. Adenosine is the first drug of choice as it is safe and terminates the majority of paroxysmal SVT [14], and if it fails metoprolol may be given intravenously. Cardioversion is recommended if a patient presents with preexcited AF [5].

Prophylactic antiarrhythmic drug therapy should be used only if symptoms are frequent, intolerable, or if the tachycardia causes hemodynamic compromise. Selective β-blocking agents (exception for atenolol), verapamil or digoxin, are the first-line agents although the 2 later drugs should not be used in patients with Wolff–Parkinson–White syndrome because of increased risk of rapid accessory pathway conduction during AF [5]. If ineffective, flecainide or propafenone may be used [5]. Catheter ablation may be performed safely in selected cases [9,15].

Focal atrial tachycardia during pregnancy is generally more challenging with respect to their frequent drug resistance, tendency to be persistent, and association with tachycardia-induced cardiomyopathy. Adenosine may be used to aid in diagnosis by causing AV block and may

TABLE 74.2 Recommendations for drug use in pregnancy.

Antiarrhythmic drugs—Vaughan Williams classification	FDA category	Placenta permeable (+, −)	Transfer to breast milk (fetal dose) (+, −)	Adverse effects
Class IA				
Quinidine	C	+	+[b]	Thrombocytopenia, premature birth, VIIIth nerve toxicity
Procainamide i.v.	C	+	+	Unknown, lupus like syndrome if long-term use, TdP (limited experience)
Disopyramide	C	+	+[b]	Uterus contraction, TdP
Class IB				
Mexiletine	C	+	+[b]	Fetal bradycardia, CNS adverse effects
Lidocaine i.v.	C	+	+[b]	Fetal bradycardia, acidosis, central nervous system toxicity
Class IC				
Flecainide	C	+	+[b]	Unknown (limited experience)
Propafenone	C	+	?	Unknown (limited experience), mild β-blocking effect
Class II (β-blocker)				
Bisoprolol	C	+	+	Bradycardia and hypoglycaemia in fetus
Metoprolol	C	+	+[b]	Growth retardation, bradycardia, and hypoglycaemia in fetus
Propranolol	C	+	+[b]	Growth retardation, bradycardia, and hypoglycaemia in fetus
Nadolol	C	?	+	Fetal bradycardia and hypoglycaemia. Animal data: evidence of embryo- and fetotoxicity in rabbits, but not in rats or hamsters, at doses 5–10X MRHD; no teratogenic potential was observed in any of these species
Atenolol[a]	D	+	+	Hypospadias (1st trim); birth defects, low birth weight, bradycardia, and hypoglycaemia in fetus (2nd, 3rd trim)
Class III				
Dronedarone	X	Contraindicated	Contraindicated	TdP rare
Sotalol	B	+	+[b]	Bradycardia and hypoglycaemia in fetus (limited experience), TdP
Amiodarone	D	+	+	Thyroid insufficiency (9%), hyperthyroidism, goiter, bradycardia, growth retardation, premature birth
Ibutilide i.v.	C	?	?	TdP (limited experience)
Vernakalant i.v.		?	?	No experience of use in pregnancy

Continued

TABLE 74.2 Recommendations for drug use in pregnancy.—cont'd

Antiarrhythmic drugs—Vaughan Williams classification	FDA category	Placenta permeable (+, −)	Transfer to breast milk (fetal dose) (+, −)	Adverse effects
Calcium channel blocker (class IV)				
Diltiazem	C	−	+[b]	Possible teratogenic effects
Verapamil oral [a]	C	+	+[b]	Well tolerated, maternal hypotension,(limited experience during pregnancy)
Verapamil i.v.	C	+	+[b]	Intravenously use may be associated with a greater risk of maternal hypotension and subsequent fetal hypoperfusion and bradycardia, heart block
Others				
Adenosine i.v.[c]	C	−	−	No fetal adverse effects reported (limited human data) dyspnea, bradycardia
Digoxin[d]	C	+	+[b]	Serum levels unreliable, safe

−, No; +, yes; ?, unknown.
[a]*Atenolol is classified D by FDA.*
[b]*Breastfeeding possible if the mother is treated with the drug [25].*
[c]*Adenosine: most experiences are in the second and third trimesters.*
[d]*Digoxin: extensive experience and therefore considered to be the safest antiarrhythmic drug during pregnancy. A prophylactic antiarrhythmic efficacy has never been demonstrated.*

also terminate AT in 30%. Electrical cardioversion is in general not recommended due to recurrence of tachycardia.

β-blocking agents, verapamil, and/or digitalis are recommended for rate control. Flecainide or propafenone may be considered if these agents fail. Catheter ablation may be considered in drug-resistant and poorly tolerated cases [9,15].

Atrial flutter and AF can lead to a rapid ventricular response with serious hemodynamic consequences for both the mother and the fetus. Electrical cardioversion should be performed for hemodynamically unstable episodes and whenever the risk of ongoing AF is considered high for the mother or the fetus [4]. In stable patients with structurally normal hearts, atrial flutter and AF can usually be terminated by intravenous ibutilide or flecainide, but the experience during pregnancy is very limited [16]. There is even less or no experience of intravenous propafenone and vernakalant for pharmacological conversion of AF during pregnancy, so these drugs may only be considered if all other attempts at cardioversion fail. Cardioversion, irrespective of technique, should be preceded by anticoagulation as recommended in pregnancy [4].

Controlling the ventricular rate with AV nodal−blocking drugs should be considered. β-blockers are recommended as first choice for rate control. Digoxin can also be used but is less effective during exercise. Digoxin blood concentrations are unreliable in pregnancy because of interference with immunoreactive serum components [17]. Nondihydropyridine calcium channel antagonists (verapamil, diltiazem) are the second choice of drugs.

Indications for prophylactic antiarrhythmic drugs relates to the severeness and frequency of symptoms [18]. Rhythm rather than rate control strategies should be considered as the preferred management of AF during pregnancy [4]. Prophylactic antiarrhythmic drugs (flecainide, propafenone) may be considered in the case of severe symptoms despite rate-controlling drugs [4]. Flecainide and propafenone should be combined with AV nodal−blocking agents. Dronedarone should not be used during pregnancy. Amiodarone should only be used in the setting of life-threatening arrhythmias if other options fail, due to its fetotoxic effects. Cavotricuspid isthmus ablation of typical atrial flutter can be performed with low radiation exposure [9], while catheter ablation of other macroreentry tachycardias and AF ablation has no role during pregnancy.

The thromboembolic risk in AF depends on the presence of risk factors for stroke and should for nonvalvular AF be assessed with the CHA_2DS_2-VAS_C score and the choice of the anticoagulant depends on to the stage of pregnancy [4].

Antiarrhythmic drugs for ventricular tachycardia

Idiopathic right ventricular outflow tract (RVOT) tachycardia, which is the most frequent VT, should be treated using either verapamil or a β-blocking agent as prophylaxis if associated with severe symptoms or hemodynamic compromise [19,20]. Sotalol or class IC antiarrhythmic drugs may be considered in the absence of structural heart disease if β-blocking agents fail. Catheter ablation of idiopathic RVOT tachycardia may be considered if drug treatment fails.

β-blocking agents are recommended both during pregnancy and postpartum in patients with LQTS due to substantial risk of cardiac arrest during that period [21], and it is also recommended in patients with catecholaminergic polymorphic ventricular tachycardia [20].

The choice of prophylactic antiarrhythmic drug therapy relates to the presence of underlying structural heart disease and LV function.

For acute treatment of VT with hemodynamic instability, immediate electrical cardioversion is recommended. Timely restoration of sinus rhythm is desirable even if the VT is well tolerated and can be achieved with electrical cardioversion or in selected cases overdrive pacing. In women with non−long QT-related sustained VT and a stable hemodynamic situation, intravenous sotalol or lidocaine acutely can be considered to terminate the tachycardia. In patients with stable monomorphic VT intravenous, procainamide may be considered. Intravenous amiodarone should only be considered for patients with life-threatening situations when other therapies have failed. Prophylactic therapy with a β-blocking agent, such as metoprolol, should be considered. Sotalol may be considered if β-blocking agents are ineffective. ICD implantation should be considered if necessary for protection of maternal life [11]. Management of cardiac arrest in pregnancy is described elsewhere [22].

Arrhythmias in congenital heart disease

Arrhythmias requiring treatment develop in mean 5% of patients with CHD during pregnancy [23]. Clinically important arrhythmias such as atrial flutter is markedly increased in women with CHD (198.8/100,000) but rare in those without [24]. Episodes of particularly atrial flutter are not well tolerated and can cause fetal hypoperfusion. Direct current conversion should be performed to restore sinus rhythm. Digoxin can be used to control ventricular rate, but has no prophylactic antiarrhythmic effect. β-blocking agents, class I antiarrhythmic drugs, and sotalol should be used with caution if the systemic ventricular function is impaired. Amiodarone should only be used when other therapies have failed.

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Part XVII

Device-based therapies

Chapter 75

Antibradycardia pacing

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The use of permanent pacemakers is steadily increasing, as reflected in a 56% increase in total implantations between 1993 and 2009. There were approximately 2.9 million pacemakers implanted during that time frame. Patients needing pacemakers are becoming older and have more medical comorbidities [1]. Potential sex-related differences in cardiac device implantations, including clinical outcomes and complications, have not been well studied. This chapter will review and summarize salient findings on sex differences in the indications, clinical outcomes, and complications related to antibradycardia pacing, along with future directions and other considerations.

Indications for permanent pacing and patient characteristics

Sex differences in patients receiving pacemakers for the treatment of bradycardia were recently reviewed in several documents, including a consensus document of the European Heart Rhythm Association [2] and a review by Elango and Curtis [3]. The main indications for permanent pacemaker implantation in women are sick sinus syndrome (SSS) and atrial fibrillation (AF) with bradyarrhythmias. A retrospective analysis by Nowak et al. included a total of 17,826 patients in Germany undergoing primary pacemaker implantation. The authors reported that the main indication for permanent pacemaker implantation in men was atrioventricular (AV) block. Men were also noted to have fascicular block significantly more often compared to women, which may predispose men to more advanced AV block [4]. In this analysis, the mean age of the patient cohort was 75.5 ± 10.4 years, with an age range of 1−104 years and a sex ratio of 47.2% women and 52.8% men. Women were older than men at the time of initial pacemaker implantation, with the mean age of women being 77.3 ± 10.2 years versus 74.0 ± 10.4 years in men ($P < .01$).

The data from currently existing registries and randomized controlled trials also indicate that women are more susceptible to sinus node dysfunction as the primary cause of bradyarrhythmias [5,6], whereas high-grade AV block is a more common indication for pacing in men [7,8]. Guha et al. evaluated 328,670 patients with SSS complicated by AF identified from the National Inpatient Sample dataset between 2003 and 2013 in a retrospective analysis. This study compared patients who underwent pacemaker implantation (87.4%) to those who did not undergo implantation (12.6%). Among the patients who received pacemakers, 54.2% were women. Variables associated with a lower likelihood of pacemaker implantation included female sex along with socioeconomic status. In a study by Toff et al. of pacemaker implantations for AV block, men accounted for 57% of implantations [7].

Congenital complete AV block occurs in 1 out of 20−22,000 births. It is usually associated with maternal antibodies to Ro (SS-A) and La (SS-B) and maternal lupus erythematosus and shows a 60% preponderance in women. On the other hand, and consistent with other studies, acquired complete AV block has a 60% preponderance in men, occurring most commonly in their 70s.

Bussink et al. studied the incidence, predictors, and outcomes of right bundle branch block (RBBB) and incomplete RBBB in 18,441 participants included in the Copenhagen City Heart Study. Patients were enrolled from 1976 to 2003 and followed through registry linkage until 2009 for all-cause mortality and cardiovascular outcomes. Participants who were included were free from previous myocardial infarction, chronic heart failure, and left bundle branch block at enrollment. The prevalence of RBBB/incomplete RBBB was higher in men (1.4%/4.7% in men vs. 0.5%/2.3% in women, $P < .001$). Significant predictors of newly acquired RBBB were male sex, increasing age, and high systolic blood pressure. RBBB was associated with significantly increased all-cause and

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cardiovascular mortality in both sexes with age-adjusted hazard ratios (HR) of 1.31 (95% confidence interval [CI], 1.11−1.54) and 1.87 (95% CI, 1.48−2.36). RBBB was associated with an increased risk of pacemaker insertion with an HR of 2.17 (95% CI, 1.22−3.86) [9].

Device mode selection

Despite various society guideline recommendations, sex differences in device pacing mode selection persist. Several studies have evaluated the relationship of sex differences in cardiac device selection. Schuppel et al. examined over 15,000 patients between 1992 and 1993 in a retrospective analysis of a large database from Germany [10]. The probability of receiving a single-chamber, dual-chamber, or rate-responsive pacemaker in relation to sex was examined. Univariate analysis showed that women were more likely to receive single-chamber pacemakers and less likely to receive dual-chamber or rate-responsive systems than men. After adjustment for demographic and clinical variables, women were still more likely to receive a single-chamber system (atrial pacing: odds ratio [OR] 0.89, 95% CI 0.74−1.07; ventricular pacing: OR 0.85, 95% CI 0.80−0.92) and less likely to receive a dual-chamber (OR 1.20, 95% CI 1.12 to 1.30) or a rate responsive system (OR 1.26, 95% CI 1.17 to 1.37) than men [10]. This finding is consistent with the above-mentioned preponderance of AV block in men, necessitating the use of dual-chamber devices.

Although the study mentioned above found sex differences in pacemaker mode selection, Roeter et al. reached a different conclusion. This study evaluated pacemaker mode selection in patients undergoing their first implantation in the Netherlands in over 39,000 patients between 1988 and 1997. This study did not find significant sex differences in pacemaker mode selection. Rather, physicians selected pacemakers by age, not sex [11]. A similar finding of no significant sex differences in pacemaker mode selection was reported in another single-center, retrospective analysis of 127 patients [12].

Therefore, the studies that indicate sex differences in pacemaker mode selection may be driven by the preponderance of advanced AV block in men as the primary indication for permanent pacemaker implantation, thus preserving AV synchrony.

Clinical outcomes

Women have been reported to survive longer after pacemaker implantation despite a higher mean age at the time of implantation [13] (Fig. 75.1). A longitudinal study with 30 years of follow-up in 6505 patients found that women had significantly longer survival than men (118 vs. 91.7 months, $P < .0001$) despite a higher age at implantation (73.2 vs. 71 years, $P < .0001$) [13]. Another retrospective single-center study by Debski et al. evaluating 1049 consecutive patients with DDD pacemakers implanted between 1984 and 2002 with follow-up until 2014 reported a 1.5-year longer average follow-up for women compared with men, although women were implanted at an older age (64.7 vs. 62.6 years) [6].

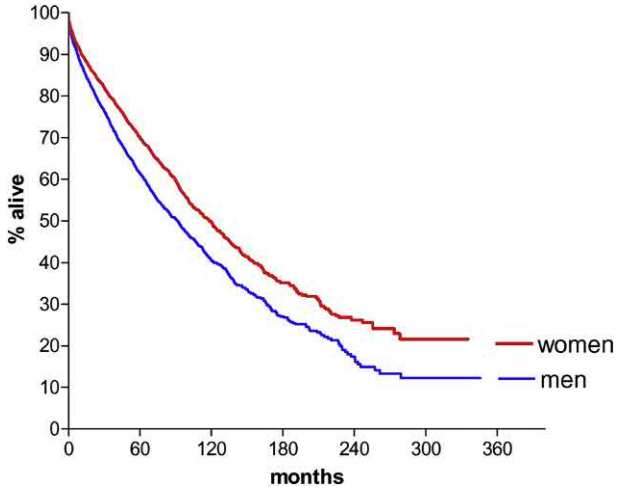

FIGURE 75.1 Kaplan−Meier analysis of survival according to sex. Despite the higher age of women (n = 3097, age: 73.2 years ± 11.3) compared to men (n = 3418, age: 71.0 years ± 12.4, $P < .0001$) at pacemaker implantation, the overall median survival time after implantation was significantly longer: 118.0 versus 91.7 months in men ($P < .0001$). *Modified with permission from Brunner M, Olschewski M, Geibel A, Bode C, Zehender M. Long-term survival after pacemaker implantation. Prognostic importance of gender and baseline patient characteristics. Eur Heart J 2004;25(1):88−95.*

Women have been well represented in randomized trials of pacing mode (Table 75.1). The proportion of women represented in these clinical trials ranged from 41% to 64% [2,7,14−16]. Event rates for major outcomes including all-cause mortality were similar between women and men. The Canadian Trial of Physiological Pacing (CTOPP) trial comparing ventricular versus physiological pacing in patients with symptomatic bradycardia found similar event rates for stroke or cardiovascular death in women compared to men. The Mode Selection (MOST) trial randomized 2010 patients with symptomatic bradycardia secondary to SSS to DDDR versus VVIR pacing. The investigators reported similar event rates for death, stroke, or heart failure hospitalization in women and men. The rate of all-cause mortality was found to be similar in women compared to men in the United Kingdom Pacing and Cardiovascular Events trial, which evaluated VVI versus VVIR versus DDD pacing in patients with symptomatic bradycardia secondary to AV block. The Danish Multicenter Randomized Study on AAI versus DDD Pacing in Sick Sinus Syndrome trial, a study of AAIR versus DDDR pacing in patients with symptomatic bradycardia secondary to SSS, also found no sex difference in survival.

TABLE 75.1 Sex and cardiovascular outcomes in randomized clinical trials for pacing mode.

Study	Design	Females, n (%)	Age (years)	Outcomes HR (9S% CI)
CTOPP[14]	Ventricular versus physiological pacing in patents with symptomatic bradycardia	1057 (41)	73 ± 10	Stroke or CV death[a] F: 0.83 (0.61−116), M: 0.96 (0.74−1.23)
MOST[16]	DDDR versus VVIR in patients with symptomatic bradycardia secondary to SND	955 (47.5)	74 (IQR 67−80)	Death, stroke, or HF hospitalization. F: 0.89 (0.71−1.13), M: 0.91 (0.73−1.15)
UKPACE[7]	VVI versus VVIR versus DDD pacing in patients with symptomatic bradycardia secondary to AV block	870 (43.0)	80 ± 6	All-cause mortality. F: 1.02 (0.81−1.29), M: 095 (0.80−1.14)
DAN PACE[15]	AAIR versus DDDR in patients with symptomatic bradycardia secondary to SND	913 (64 5)	73 ± 11	All-cause mortality. F: 1.08 (0.86−1.37), M: 0.98 (0.69−1.40)

AAIR, atrial rate adaptive pacing; *CI*, confidence interval; *CTOPP*, Canadian Trail of Physiologic Pacing; *DANPACE*, Danish Multicenter Randomized Trial in Single-Lead Atrial Pacing versus Dual-Chamber Pacing in Sick Sinus Syndrome; *DDDR*, dual-chamber rate adaptive pacing; *F*, female; *HF*, heart failure; *HR*, hazard ratio; *IQR*,interquartile range; *M*, male; *MOST*, Mode Selection Trial; *SND*, sinus node dysfunction; *UKPACE*, United Kingdom Pacing and Cardiovascular Events; *VVI*, ventricular pacing; *VVIR*, ventricular rate-adaptive pacing.
[a]*Estimated from Fig. 3 Connolly et al.*[14].
Used by permission from Linde C, Bongiorni MG, Birgersdotter-Green U, Curtis AB, Deisenhofer I, Furokawa T, et al. Sex differences in cardiac arrhythmia: a consensus document of the European heart Rhythm association, endorsed by the heart Rhythm society and Asia Pacific heart Rhythm society. Europace. 2018;20(10):1565−ao. (permission pending).

Improvement in quality of life (QOL) has been studied in patients who received permanent pacemakers for bradyarrhythmias [17,18]. Significant sex differences were not found in the CTOPP trial [19], whereas higher QOL scores were reported in men in the MOST trial [20]. In the CTOPP trial, QOL was measured in a substudy of 269 patients with detailed QOL measures at baseline and 6 months after implantation. There was also an assessment of QOL in the parent study in 1721 patients with a 12-item QOL instrument package. Neither evaluation showed any differences in QOL between women and men. A longitudinal analysis of serial QOL measures in the MOST trial found that pacemaker implantation resulted in higher QOL scores and improved functional status in men compared to women.

Complications

Complications from cardiac implantable devices including permanent pacemakers have been increasing as more high-risk patients with comorbidities are undergoing implantation. The burden of such complications, including hematoma, infection, and pneumothorax among others, has a significant impact on QOL, morbidity and mortality, and societal cost [21,22]. Investigations into sex differences in complications from pacemaker implantation have found conflicting results [4,6].

The previously mentioned large retrospective trial by Nowak et al. examined sex differences in complications after pacemaker implantation. The complication rates for both sexes are shown in Table 75.2. Women had significantly more complications than men (5.8 vs. 4.7%; OR 1.3; 95% CI 1.1−1.5), independent of age or pacing system implanted. Although women had more complications with cephalic and subclavian vein access, the difference reached statistical significance only for cephalic vein access. With regard to specific types of complications, differences

TABLE 75.2 Complications according to sex (in %).

Complications	Female	Male	*P*-value
N	8421	9405	
Single-chamber implant	4.9	3.7	<0.01
Dual-chamber implant	6.4	5.2	<0.01
Cephalic vein	5.5	4.3	<0.01
Subclavian vein	6.5	5.4	n.s.
Asystole	0.39	0.32	n.s.
Ventricular fibrillation	0.12	0.14	n.s.
Pneumothorax	0.74	0.35	<0.01
Pocket hematoma	0.87	0.58	<0.01
Hematothorax	0.07	0.02	n.s.
Lead dislocation	2.30	2.31	n.s.
Device infection	0.10	0.12	n.s.
Others	0.93	0.70	n.s.
All complications	5.79	4.74	<0.01

used by permission from Nowak et al. Europace, 2010. **12**(2): p. 210−5. (permission pending − reference 4).

between women and men were observed for pneumothorax and pocket hematoma. For pneumothorax, women had an OR of 2.12 (95% CI 1.39−3.24) and subclavian puncture an OR of 4.02 (95% CI 1.91−8.45) compared to men. For pocket hematoma, women had an OR of 1.49 (95% CI 1.05−2.11), while venous access had no statistically significant influence [4]. This suggests pneumothorax in women may be related to a higher risk of complications from subclavian puncture compared to cephalic access.

Despite clear sex differences noted in the study above, a more recent evaluation by Debski et al. did not find significant differences between women and men in the rates of complications. The rate of adverse events was similar in both sexes, including lead malfunction and infectious complications [6].

The US Food and Drug Administration approved a new modality of pacing in 2016, a transcatheter leadless pacemaker, currently only available as a single-chamber VVIR system. The safety and efficacy of this type of pacing has been well established [23,24]. The overall rate of complications and specific complications such as pocket infection, hematoma, and pneumothorax are significantly lower due to the difference in insertion technique. However, cardiac perforation/pericardial effusion is a significant potential complication. High-risk features for cardiac perforation/effusion include female sex, small body mass index, chronic obstructive pulmonary disease, and congestive heart failure. The higher risk for cardiac perforation after implantation of transcatheter leadless pacemakers in women is suspected to be due to their generally smaller size.

Special considerations

As discussed by Giudici et al., device placement in women has unique considerations not addressed with standard implant techniques, such as irritation and discomfort from purse straps, bra straps, and automobile restraints. Young women may also have excessive scar formation due to skin tension. There are often body image concerns as the subclavian region is often exposed with commonly worn clothing. Patients may request a specific location at the time of a new implant or pocket revision/relocation of the device pocket due to the appearance and/or discomfort of the pocket. To address these concerns, several options are available, including a low incision, the submammary technique, or leadless pacemaker implantation. Submammary device placement addresses these problems and is associated with greater patient comfort, cosmetics, and device acceptance (Fig. 75.2). [25] In their phone survey of patients who underwent submammary implantation, 11% felt the implant made mammography more uncomfortable, while 89% did not feel any difference. The authors also gave the Florida Patient Acceptance Survey (FPAS) to all their submammary

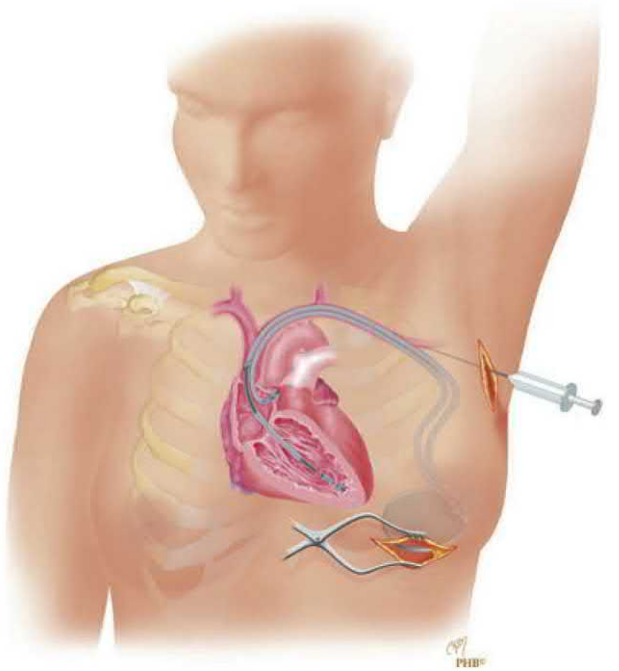

FIGURE 75.2 Two incision technique for submammary pacemaker implantation. A small anterior axillary incision is made to obtain axillary access and initial lead placement. Then, a submammary incision is made with deep dissection down to the rib to allow placement of the generator, which is connected to the tunneled leads. *Published with permission (permission pending) from Guidici et al. J Cardiovasc Electrophysiol, 2013. 24(4): p. 476−9.*

implant patients as a more formal psychological instrument that has been used to assess the impact of device placement in women. Women with submammary implant reported significantly greater device acceptance ($M = 92.41$, $SD = 6.46$) than women with a standard implant technique ($M = 70.29$, $SD = 17.85$); $t(54) = -6.08$, $P < .001$, on the FPAS. Across subscales on the FPAS, women with submammary implant also reported significantly less body image concerns ($P < .001$), less device-related emotional distress ($P < .001$), and greater confidence in returning to life appropriately ($P = .01$) than women with standard device placement [25].

Another option in such situations is the use of a leadless pacemaker as mentioned above. Since FDA approval of the Micra transcatheter leadless pacemaker system in 2016, the use of this device is increasing (Fig. 75.3) [26]. A large postmarket study by El-Chami et al. published in 2018 reported on the safety and feasibility of this device. Pacing thresholds were low and stable through 12 months postimplantation [24]. There are no data currently on any sex differences in complications or outcomes with leadless pacemakers. The sheer absence of a surgical pocket alleviates any cosmetic concerns as well as any discomfort specifically related to a surgical pocket during mammography.

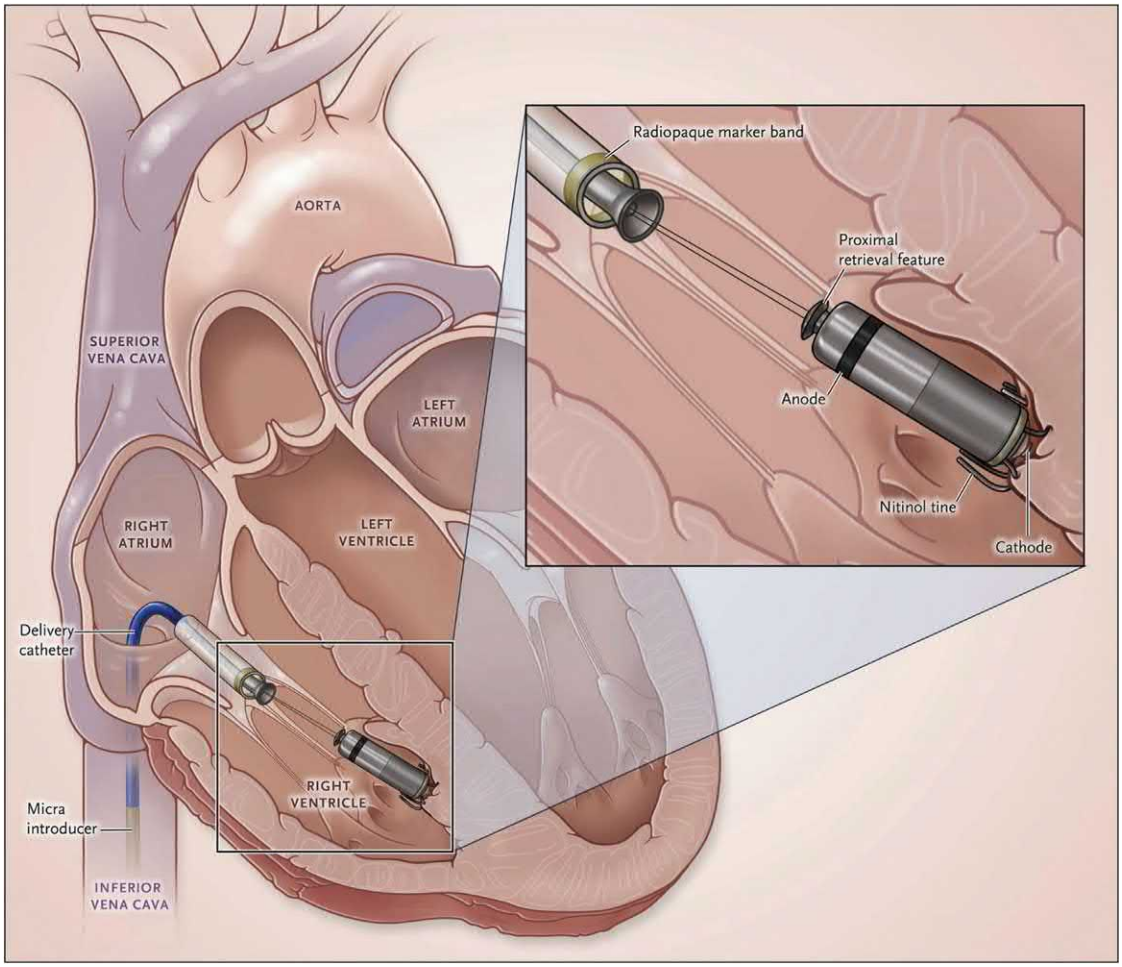

FIGURE 75.3 Micra transcatheter pacing system positioned in the right ventricle. *Published with permission (permission pending) from Reynolds DW, Ritter P. A leadless Intracardiac transcatheter pacing system. N Engl J Med 2016;374(26):2604–5.*

Careful and detailed discussion tailored to a patient's special needs and desires in sex-specific situations should take place prior to implantation of any cardiac implantable electrical device.

Summary

There are sex differences in the indications, outcomes, and especially complications for pacemaker implantation. Understanding these differences will improve the chances for optimal outcomes from pacemaker implantation regardless of sex.

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Chapter 76

Primary and secondary prevention of sudden cardiac death in women

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Epidemiology of sudden cardiac death

Sudden cardiac death (SCD) is commonly defined as sudden death caused by cardiac disease within 1 h of symptom onset and lacking another cause of death [1]. SCD is the leading cause of death in the United States and accounts for 1.3 million years of potential lives lost in women and 2.0 million in men [2]. As depicted in Fig. 76.1, it is a greater cause of premature death in women than all individual cancers [2]. As SCD commonly occurs in ages < 70 years, efforts to reduce SCD have the potential to reduce premature mortality [1].

The incidence of SCD has repeatedly been shown to be significantly lower in women compared with men [1−3]. Data from the Framingham Heart Study in >15,000 participants without cardiovascular disease showed that the remaining lifetime risk of SCD was more than twice as high in men (10.1%−11.2%) compared with women (2.3% −3.4%) across all studied age groups [1]. The difference in incidence between the sexes shows a narrowing discrepancy in elderly and is obliterated in those aged >85 years where the male:female ratio is 1:1 [4,5]. As could be expected, the incidence of SCD increases with age, and only < 1% occurs in adults aged below 35 years. In absolute numbers, few SCD occurs <35 years of age, but the proportion of SCD is higher [6].

Women who die from SCD have been shown to be significantly older: 70.1 years versus 63.5 years in a Finnish study, and 82.4 versus 70 years in a US study [3,4]. The reason for a lower risk of SCD in women, which appears to diminish with age, is not completely understood. Mechanisms such as the protective effect of estrogen have been suggested. In the Heart and Estrogen/Progestin Replacement Study (HERS), the use of hormone replacement therapy in postmenopausal women with established coronary disease did not reduce coronary heart disease nor resuscitated cardiac arrest compared with placebo. In contrary, there was an increase in coronary heart disease in the first year after initiation of hormone replacement therapy [7]. This risk decreased with time, and during years 4 and 5 in the study, women who receive hormone replacement therapy had a lower risk of coronary heart disease. It was speculated that an early negative effect of hormone replacement therapy could in the long-term be outweighed by a slower positive effect on atherosclerosis mediated by lower cholesterol levels. Hence, women not on hormone replacement therapy in the HERS were advised not to initiate therapy, whereas women already on hormone replacement therapy were informed that they might benefit from the treatment due to a delayed positive effect [7]. Many women in the HERS trial followed this advice and were followed in the HERS II trial. However, the long-term benefit of hormone replacement therapy on cardiovascular events was not confirmed in the HERS II trial. There was an increased risk of nonfatal ventricular arrhythmia in the group receiving hormone replacement therapy, but there was no increase in sudden death [8].

Comparisons of sudden cardiac death on a global level are difficult due to differences in the definition, a low percentage of autopsies, and a lack of data from several continents. A review of 67 studies on out-of-hospital cardiac arrests included 60 studies from Europe, the United States, and Australia and 7 studies from Asia and detected 10-fold variances in outcomes. There were no studies from Africa or South America [9]. In this review, the United States had the highest incidence of out-of-hospital arrest of presumed cardiac origin (55%) compared with Australia (44%), Europe (35%), and Asia (28%). The percentage of VF and survival was lowest in Asia [9].

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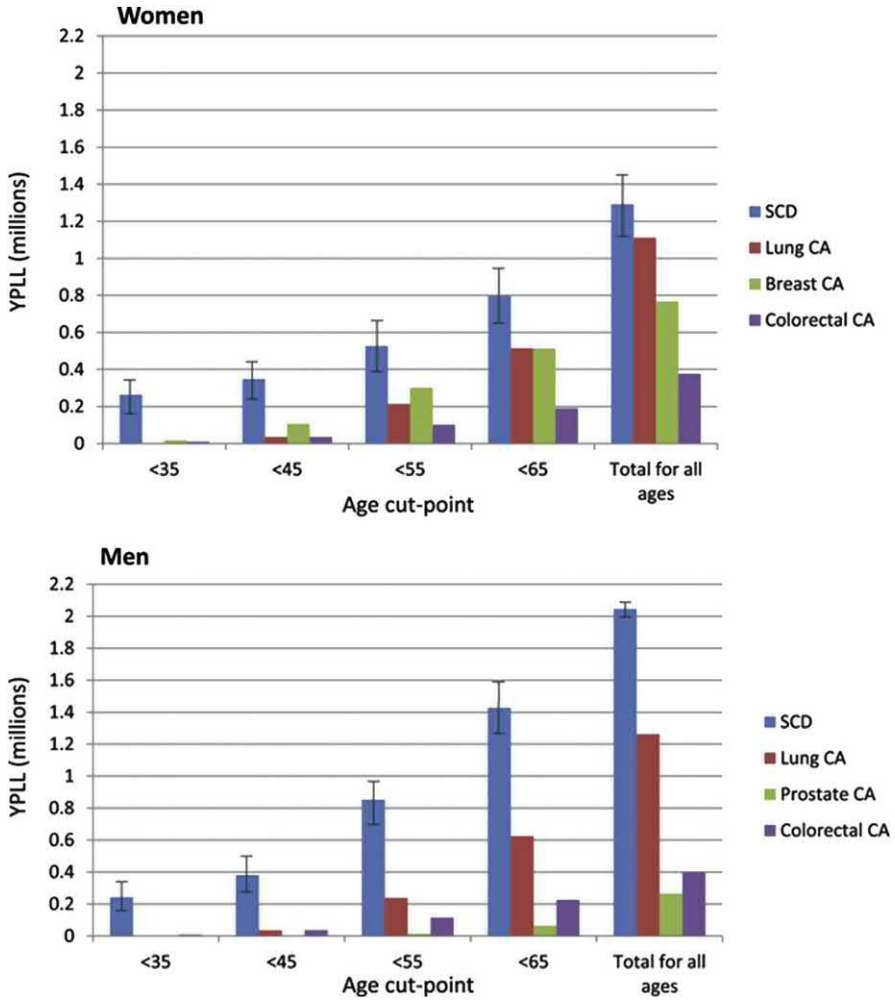

FIGURE 76.1 Years of potential life lost among women from sudden cardiac death in the United States compared to most common cancer disease by Stecker EC, Reinier K, Marijon E, Narayanan K, Teodorescu C, Uy-Evanado A, et al. Public health burden of sudden cardiac death in the United States. Circ Arrhythm Electrophysiol 2014;7(2):212–217. https://www.ahajournals.org/journal/circep an American Heart Association journal. Reprinted with permission from Wolters Kluwer Health, Inc.

In summary, sudden cardiac death is more common in men than in women, although the sex difference decreases with age. It has been speculated that this is due to the protective effect of estrogen in younger women, but data on hormone replacement therapy have not demonstrated a reduced cardiovascular disease or death. Data on SCD are mainly reported from Europe, the United States, and Australia.

Causes of sudden cardiac death

The most common cause of SCD is coronary heart disease. SCD due to a fatal arrhythmic event secondary to coronary heart disease can occur at the time of a myocardial infarction or postinfarction in the presence of alterations in the myocardium.

Coronary heart disease is the most common cause of SCD in both sexes, although more commonly so in men compared with women [10,11]. In the large Finnish study, Fingesture, of 5869 subjects, who died of SCD and underwent autopsy, significantly more men had ischemic heart disease (75.7%), compared with women (71.7%) [3]. Even when accounting for predisposing conditions such as myocardial infarction and heart failure, women have a lower incidence of SCD than men [6].

Apart from coronary heart disease, the causes for SCD are diverse, particularly in the younger population (Fig. 76.2).

The risk of SCD in women correlated with the severity of ischemic heart disease in the Framingham Heart Study, where women who had sustained a myocardial infarction had twice as high risk of SCD compared with women with

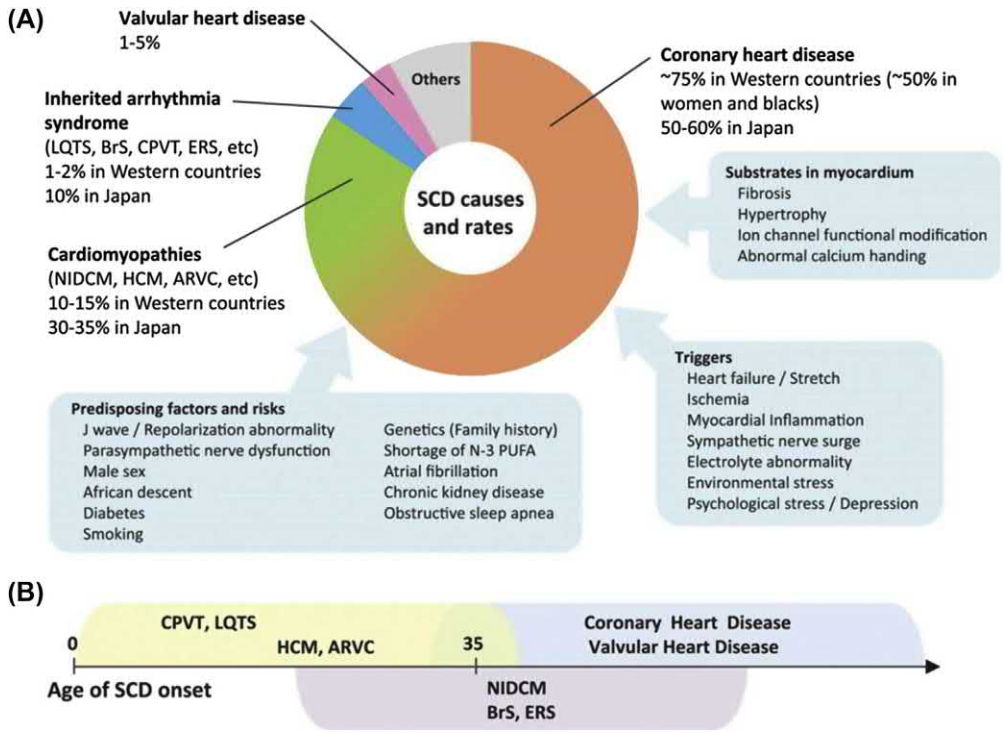

FIGURE 76.2 (A) Causes of sudden cardiac death. (B) Causes of sudden cardiac death in relationship to age by Hayashi M, Shimizu W, Albert Christine M. The spectrum of epidemiology underlying sudden cardiac death. Circ Res 2015;116(12):1887−1906. https://www.ahajournals.org/journal/res Circulation Research is an American Heart association (AHA) journal. *BrS*, Brugada syndrome; *CPTV*, catecholaminergic polymorphic ventricular tachycardia; *ERS*, early repolarization syndrome; *HCM*, hypertrophic cardiomyopathy; *LQTS*, long-QT syndrome; *NIDCM*, non−ischemic dilated cardiomyopathy; *PUFA*, polyunsaturated fatty acid; *RVC*, arrhythmogenic right ventricular cardiomyopathy. *Reprinted with permission from Wolters Kluwer Health Inc.*

angina [5]. Similar risks have been shown in the Nurses' Health Study, where the risk of SCD was increased in fourfold in women with a prior myocardial infarction [12].

Although it is well known that individuals with ischemic heart disease have an increased risk of SCD, most cases of SCD happen in individuals with no prior clinical manifestation of their disease or in patients with known coronary artery disease that has been regarded as low risk [6,10]. SCD might hence be the first manifestation of coronary heart disease [6]. Most women suffering SCD have no prior history of heart disease, and structurally normal hearts are a more common finding in women autopsied after SCD [5,12,13].

There has been a decline in the incidence in coronary heart disease during the past 50 years, and SCD due to ischemic heart disease is decreasing in parallel in both men and women [14].

Although SCD due to ischemic heart disease is decreasing, SCD due to nonischemic causes is increasing in both men and women. In the Fingesture trial, women were more likely than men to have a nonischemic cause of death (28.3% in women, compared with 24.3% in men) [3]. As women more commonly sustain SCD due to nonischemic causes, the overall decline in incidence of SCD has been slower in women compared with men [3]. It has even been shown in a US study of younger women aged 35−44 years that there was an increase in age-specific death rates [4]. In a smaller autopsy study aimed at determining cause of death in younger women with SCD, aged 35−44 years, the underlying cause was not clear in 50% of women despite extensive investigation, compared with 24% in age-matched men [13]. This may be due to a more multifactorial disease pattern in women, or a yet unknown cause of SCD in younger women.

In summary, the majority of SCD also occurs in patients considered at low or moderate risk or those without known risk factors [15]. The combination of dearth of symptoms and lack of high-risk features in the largest group of individuals suffering from SCD makes prevention of SCD challenging. The reduction of incidence in women has been slower compared with men, and in some age groups, an increasing trend has been seen, suggesting other mechanisms for SCD in women.

Primary prevention

Risk factors for sudden cardiac death in women

In the Nurses' Health Study, current smokers of ≥25 cigarettes/day had the highest modifiable risk for SCD with a hazard ratio (HR) of 4.13 (95% CI of 2.69−6.33). In women with diabetes, the risk was also increased with an HR of 2.93 (95% CI of 2.13−4.04) after multivariable analysis. The risks were also increased in women with hypertension with an HR of 2.49 (95% CI of 1.87−3.32) [12]. Self-reported hypercholesterolemia did not confer an increased risk of SCD in the Nurses' Health Study [12]. This is in contrast with results from the Framingham Heart Study where serum cholesterol levels incurred higher risk for SCD. This increased risk of increased cholesterol levels was especially pronounced in women aged 35−64 years compared with elderly women [5]. It is possible that self-reported hypercholesterolemia underestimates the true prevalence.

In a Framingham Heart Study, cohort classic risk factors for ischemic heart disease were also associated with SCD in both sexes. Significant differences were seen in risk of SCD in women aged 45 or 55 years at their first visit with at least one or two risk factors for cardiovascular disease (hypertension, increased cholesterol levels, presence of diabetes, or current smoker) [1]. Blood pressure levels showed the strongest association with lifetime risk of SCD [1] (Fig. 76.3).

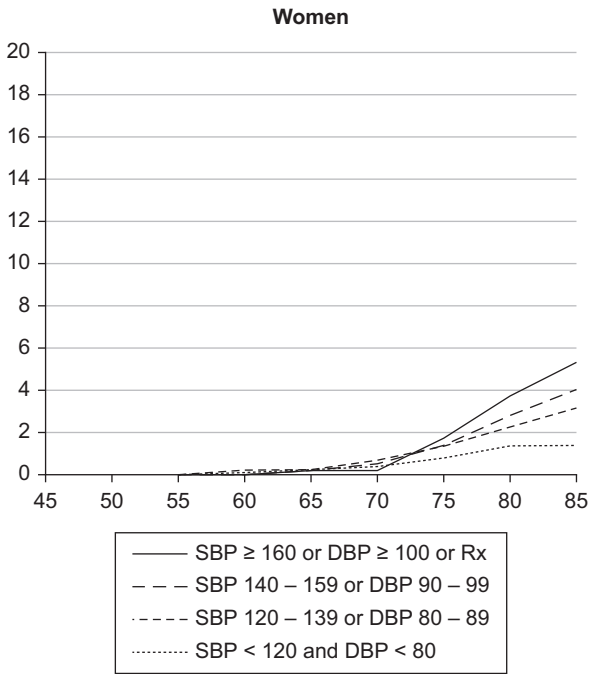

FIGURE 76.3 Lifetime risk of sudden cardiac death at index age 55 years in women stratified by blood pressure by Bogle BM, Ning H, Mehrotra S, Goldberger JJ, Lloyd-Jones DM. Lifetime risk for sudden cardiac death in the community. J Am Heart Assoc 2016;5(7). Published on behalf of the American Heart Association, Inc., by Wiley Blackwell. *Reprinted with permission from Wiley Blackwell.*

Hypertension is commonly associated with left ventricular hypertrophy (LVH). In the 2018 ESC guidelines for hypertension, LVH on ECG is considered a sign of hypertensive-mediated organ damage [16]. In a study of individuals aged > 40 years in the Framingham Heart Study, LVH was associated with increased rates of SCD in both men and women [17]. In the Finnish Fingesture trial, women who suffered SCD were more likely to show signs of left ventricular hypertrophy and myocardial fibrosis compared with men [3]. One trial has shown that reducing LV hypertrophy with antihypertensive therapy was associated with a lower risk of SCD [18].

In the Nurses' Health Study, obese women had a 1.6-fold increased risk of SCD compared with women with BMI <25, which increased to 2.5 if diabetes and hypertension were removed from the model [12]. The risk of obesity seems particularly pronounced if overweight was present already in young age (age 18 years), and women who had BMI > 30 at age 18 years had an increased risk of SCD. This was also seen if a weight gain of ≥20 kg occurred before early to middle adulthood (defined as age of 27 years in the study) [19]. Women with a BMI ≥ 35 had a significantly increased risk of SCD regardless of age, and this risk remained elevated even after adjustment for atherosclerotic mediators, indicating that risks associated with obesity may be mediated through other pathways. The association between BMI and SCD showed a J-shaped relationship, where BMI 18.5−20.9 was associated with an increased risk for SCD. The associated risk of lower BMI and SCD was not shown in the younger population, indicating that a low BMI with increasing age might be a confounder indicative of preclinical disease causing weight loss [19]. These data indicate the importance of maintaining a healthy weight for primary prevention of SCD.

In the Nurses' Health Study, the risk of SCD increased in younger women if they had a parent that had suffered myocardial infarction before the age of 60 years [12].

In summary, most SCDs are caused by ischemic heart disease. Targeting risk factors for ischemic heart disease result in reduced incidence of SCD, as shown in the Framingham Heart Study where patients without known cardiovascular disease had a decline in SCD by 39% during a 50-year time period [14]. During the same time period levels of cholesterol, systolic blood pressure and the use of tobacco declined [14]. This indicated that targeting modifiable risk factors for ischemic heart disease can reduce the risk of SCD on a population level.

Secondary prevention

Sudden cardiac death prevention in patients with established cardiovascular disease

The risk for SCD remains increased in patients with known cardiovascular disease, but it is still modifiable. The risk of SCD in participants in the Framingham Heart Study with cardiovascular disease declined with 57% from 1950–1969 to 1990–1999. The decline in men and women was almost equal. The corresponding decline for patients without known cardiovascular disease was 39% [14]. Women with established cardiovascular disease were included in the HERS trial and followed up in the HERS II trial [7,8]. In this population, exercise at least three times per week was associated with a lower risk of SCD [20]. Heart failure, myocardial infarction, reduced kidney function (glomerular filtration rate < 40 mL/min/1.73 m^2), atrial fibrillation, physical inactivity, and diabetes were all shown to be independent risk factors for SCD [20]. A combination of left ventricular ejection fraction and these clinical risk factors best predicted SCD. Women with no risk factors had a yearly risk of 0.34% compared with 2.90% in women in the highest risk group with at least three risk factors [20].

Sudden cardiac death prevention in patients with heart failure

Heart failure patients have an increased risk of SCD. Women with heart failure in the Framingham Heart Study showed a fivefold increased risk of sudden death [5]. The relative risk of SCD was equal for men and women, but the absolute risk remained higher in men (5.6/1000 vs. 16/1000) [5]. One of the most common causes for heart failure is ischemic heart disease, and the majority of the patients in the Framingham Heart Study with heart failure also had coronary heart disease [5]. For patients with heart failure, appropriate guideline recommended optimal medical therapy as well as device therapy has been shown to reduce mortality [21].

Use of implantable cardioverter defibrillator in the prevention of sudden cardiac death

ICD therapy reduces mortality in those having survived a cardiac arrest or those having sustained prolonged ventricular arrhythmias [21,22].

In patients with heart failure, reduced left ventricular ejection fraction (EF) is a risk factor for mortality and SCD [23]. Severely reduced left ventricular EF is the main clinical predictor for SCD [20]. In current guidelines, ICD therapy is recommended for symptomatic patients with heart failure, who have an EF $\leq$35% despite optimal medical therapy. In patients with prolonged QRS duration $\geq$130 ms, device therapy using cardiac resynchronization therapy (CRT) in combination with a defibrillator (CRT-D) should be considered [21,22].

In a metaanalysis of eight ICD trials, the relative risk of arrhythmic mortality was reduced with 60% in those receiving an ICD [24]. Notably, women were underrepresented in these trials, ranging from 8% to 33% of the population [24]. In a European registry study of primary prevention ICDs in 11 different countries, women constituted 19% of the population [25]. Women are less likely to receive an ICD, even after adjustment of age and comorbidities [26]. In one large study of >20,000 patients, fewer women eligible for ICD therapy received counseling compared with men. However, in women receiving counseling, implantation rate was similar to that in men [27]. In one study exploring the reasons for not receiving an ICD after referral to an electrophysiologist, men and women showed similar distributions of reasons for not implanting ICDs. Once referred to an electrophysiologist, there was no significant difference in implantation rate between the sexes [28]. Women with ICD received fewer adequate shocks (8%) compared with men (20%) in one European registry study [25]. Similar data were shown in a study of patients in Ohio of 5450 patients receiving an ICD for primary or secondary prevention, where women constituted 21%. In this study, women received significantly less adequate therapy (both antitachycardia pacing and shocks) [28] (Fig. 76.4).

In a registry study with a median follow-up of 33 months, the relative risk of death in a multivariable

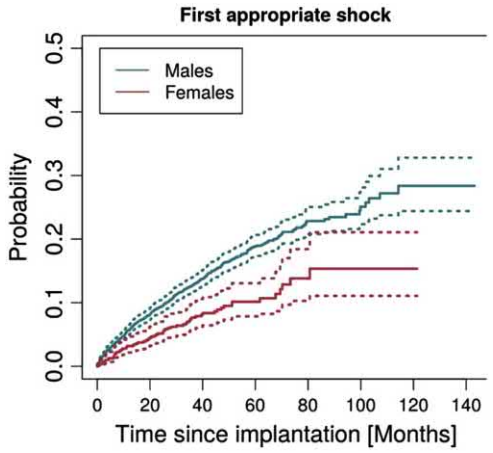

FIGURE 76.4 Cumulative incidence of first ICD shock with 95% confidence intervals by Sticherling C, Arendacka B, Svendsen JH, Wijers S, Friede T, Stockinger J et al. Sex differences in outcomes of primary prevention implantable cardioverter-defibrillator therapy: combined registry data from eleven European countries. Europace: European pacing, arrhythmias, and cardiac electrophysiology: Journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2018; 20(6):963–970. Reprinted with permission from Oxford University Press (published on behalf of European Heart Rhythm Association (EHRA)).

analysis was 35% lower in women with primary prevention ICD compared with men [25]. This differs from the results of the Ohio registry study where mortality rates did not differ between the sexes, despite women were more seldom receiving adequate therapy [28]. One metaanalysis on primary preventive ICD treatment from five ICD studies showed no survival benefit in women [29]. In a second metaanalyses, mortality was similar in both sexes, but women received significantly less appropriate ICD therapies [30]. This indicates that not all deaths in these populations are due to arrhythmic events.

To summarize, less ICDs are implanted in women compared with men, and women get fewer appropriate therapies delivered by their ICDs. Mortality benefits in women receiving ICDs are less certain than in men. More studies in women are needed to assess whom may benefit most from ICD therapy and to address the question if arrhythmic risk stratification differs between the sexes.

Response to cardiac arrests in women

In the Fingesture study, 83% of cardiac deaths in women were unwitnessed, occurring mostly indoors (92%), at night, and were rarer during exercise (2%) compared with men [3]. Similarly, in a Canadian study of out-of-hospital cardiac arrests, women had fewer witnessed cardiac arrests compared with men [31].

In witnessed cardiac arrests, bystander cardiopulmonary resuscitation (CPR) leads to increased survival, lower risk of anoxic brain damage, and fewer nursing home admission [32]. In a Danish study of those receiving bystander CPR, 80% were men, and the proportion increased to 90% men in those also receiving bystander defibrillation [32]. Likewise, a study of 10,862 out-of-hospital cardiac arrests in Canada demonstrated a lower rate of bystander CPR in women as compared with men [31]. Data from a resuscitation outcome consortium in the United States of 19,331 out-of-hospital cardiac arrests also showed that women received less bystander CPR in public, but there was no sex difference in regard to CPR in the private setting [33].

Men present more frequently with shockable arrhythmias at times of cardiac arrest [31]. In one study of the response of the emergency services called to out-of-hospital cardiac arrests in the United States, defibrillation was significantly more often used in men compared with women [34]. However, the proportion of patients with an arrhythmia that may respond to cardioversion were not reported. In one cohort study of bystander CPR in out-of-hospital nontraumatic cardiac arrest by the resuscitation outcome consortium, survival was increased in those receiving bystander CPR. Men had bystander CPR more commonly in public (45% vs. 39% in women). Bystander CPR was significantly associated with survival to hospital discharge. In this study, men had an almost 30% increased chance of survival to hospital discharge compared with women in multivariable analysis [33]. In a Danish observational study, women who suffered an out-of-hospital cardiac arrest had lower rate of survival upon hospital arrival. Women with cardiac arrest were overall older and had more chronic pulmonary obstructive disease, cancer, and psychiatric illness, whereas men were younger and more commonly had cardiovascular disease [35]. In contrast, in younger women (12−50 years) who presented with a shockable rhythm, the 30-days survival was increased compared with men [35]. In recent years, survival from out-of-hospital cardiac arrest has improved significantly, but despite these advances, absolute survival remains low (approximately 10%) [6].

It is unclear why there is a sex difference in the likelihood of receiving bystander CPR in a witnessed arrest. In a national survey performed in the United States, 548 individuals responded to a 12-question survey looking into possible reasons why women may receive more infrequent CPR. According to public perception, the reasons fell into three categories: (1) sexualization of women's bodies with fears of accusation of inappropriate touching; (2) frailty of women, fear of causing injury; and (3) misperceptions about women in acute medical distress [36].

In summary, women who suffer cardiac arrests are more commonly older and have more comorbidities than men. It is more common for women to suffer unwitnessed cardiac arrests. Women who suffer public cardiac arrests less commonly receive CPR and less commonly have a shockable rhythm. In younger women with shockable rhythm, survival is increased compared with men. Efforts to increase bystander CPR training and automated external defibrillators in, for instance, sport facilities might benefit women less than men. An ICD is indicated for secondary prevention of SCD as per current guidelines in women who have survived a cardiac arrest.

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Chapter 77

Sex differences in implantable cardioverter defibrillators: outcomes and utilization

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Sudden cardiac death (SCD) is a leading cause of death in North America and Western Europe. In the United States, the incidence of SCD is estimated to be between 180,000 and 450,000 per year [1]. The incidence of SCD has been reported to be two- to threefold higher in men compared with women [2–5]. The Framingham Heart Study reported that the lifetime risk of SCD in men ranges between 10.1% and 11.2% at index ages 45, 55, and 65 years, whereas these estimates at the same index ages for women range between 2.4% and 3.4% [2]. The majority of SCD events occurred before age 70 years.

The etiology of SCD also varies between the sexes and is reviewed in more detail in Chapters 61 and 74. Sex differences in the initial identified rhythm have been observed in patients presenting with out-of-hospital cardiac arrest. As reported in the Oregon Sudden Unexpected Death Study, men are more likely to present with ventricular tachycardia (VT) or ventricular fibrillation (VF)—rhythms responsive to ventricular antitachycardia pacing, cardioversion, or defibrillation—whereas women are more likely to present with pulseless electrical activity or asystole—rhythms potentially effectively treated by cardiac pacing [1]. Men are more likely to have coronary heart disease as the underlying substrate contributing to SCD. In contrast, women are more likely to have a dilated cardiomyopathy or valvular heart disease. Depressed left ventricular ejection fraction (LVEF) is a major risk factor for SCD.

Clinical trials of implantable cardioverter defibrillator therapy

Secondary prevention studies

Randomized clinical trials have demonstrated the safety and efficacy of the implantable cardioverter defibrillator (ICD) for prevention of premature SCD [6–8]. These trials published in 1997 and 2000 enrolled patients who presented with resuscitated cardiac arrest secondary to VF or VT with significant hemodynamic compromise (Table 77.1). These three secondary prevention trials (AVID, CASH, and CIDS) reported that the ICD reduced all-cause mortality compared with medical therapy [6–8]. The proportion of women enrolled in these trials was low (15%–20% of the study populations), and a detailed analysis of outcomes based on sex has not been done. The Canadian Implantable Defibrillator Study did not observe a statistically significant difference in overall mortality between sex [7]. In the metaanalysis of these three trials, sex differences in outcomes were not reported [9].

Primary prevention studies

A number of randomized clinical trials have investigated the role of the ICD for prevention of SCD in high-risk populations [10–15]. These primary prevention trials are summarized in Table 77.2. All subjects had significant left ventricular dysfunction and the majority of subjects had underlying coronary artery disease and a remote myocardial infarction. Overall, these studies reported that the ICD reduced mortality compared with optimal medical therapy. Enrollment of women in these trials was low (8%–29% of the study populations). Enrollment of women was highest in the DEFINITE trial (Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation) and the DANISH study (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality trial) which only included subjects with nonischemic cardiomyopathy [13,15].

Sex differences in the primary study outcomes were compared in most of these primary prevention trials.

Sex and Cardiac Electrophysiology. https://doi.org/10.1016/B978-0-12-817728-0.00077-2
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TABLE 77.1 Sex and secondary prevention ICD trials.

Study	Population enrolled	Therapy	Enrollment	Primary endpoint	Outcome
AVID [6]	Resuscitated VF, syncopal VT, VT, and LVEF ≤0.40	ICD versus amiodarone or sotalol	Men 813 (80%) Women 203 (20%)	All-cause mortality	Reduction in mortality in ICD group 39% at 1 year 27% at 2 years
CIDS [7]	Resuscitated VT or VF, syncopal VT or symptomatic VT, and LVEF ≤0.35, syncope with VT induced at electrophysiology study	ICD versus amiodarone	Men 560 (85%) Women 99 (15%)	All-cause mortality	Nonsignificant decrease in mortality in ICD group RR 19.7%, 95% CI 7.7−40, $P = .142$
CASH [8]	Resuscitated VF	ICD versus amiodarone or metoprolol	Men 230 (80%) Women 99 (15%)	All-cause mortality	Nonsignificant reduction in mortality in ICD versus drug group HR 0.766, 97.5% CI upper bound 1.11, $P = .08$

AVID, Antiarrhythmics Versus Implantable Defibrillator; *CASH*, Cardiac Arrest Study Hamburg; *CI*, confidence interval; *CIDS*, Canadian Implantable Defibrillator Trial; *ICD*, implantable cardioverter defibrillator; *LVEF*, left ventricular ejection fraction; *RR*, relative risk; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia.

TABLE 77.2 Sex and primary prevention ICD trials.

Study	Population enrolled	Therapy	Enrollment	Primary endpoint	Outcome
MADIT-I [10] (1996)	Prior MI inducible VT LVEF ≤0.35 NYHA class I and III	ICD versus medical therapy	Men 184 (92%) Women 16 (8%)	All-cause mortality	54% ↓ in death in ICD group
MADIT-II [10]	Prior MI, LVEF ≤ 30%	ICD or medical therapy	Men 1047 (85%) Women 192 (15%)	All-cause mortality	31% ↓ in death in ICD group
MUSTT [11] (1999)	CAD, LVEF ≤0.40 NYHA I and III VT induced at EPS	Medical therapy ± ICD versus no EP-guided treatment	Men 1265 (84%) Women 233 (16%)	All-cause mortality	21% ↓ in mortality ($P = .06$) in EP-guided group and ICD versus no EP-guided therapy
SCD-HeFT [12] (2005)	NYHA II or III HF ischemic or nonischemic CM, LVEF ≤ 35%	ICD or optimal medical therapy	Men 1941 (77%) Women 132 (29%)	All-cause mortality	23% ↓ risk of death in ICD group
DEFINITE [15] (2004)	NYHA I, II, or II HF nonischemic CM EF ≤ 35% PVCs or NSVT	ICD or optimal medical therapy	Men 326 (71%) Women 132 (29%)	All-cause mortality	20% ↓ arrhythmic death in ICD group nonsignificant ↓ overall mortality
DANISH [15] (2016)	NYHA II–IV Nonischemic CM EF ≤ 35%	ICD or guideline-based HF medical therapy	Men 809 (73%) Women 307 (27%)	All-cause mortality	No significant difference in all-cause mortality 50% reduction in SCD in ICD group

CAD, coronary artery disease; *CM*, cardiomyopathy; *EP*, electrophysiologic; *EPS*, Electrophysiology study; *HF*, heart failure; *ICD*, implantable cardioverter defibrillator; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *NYHAs*, New York Heart Association class; *RR*, relative risk; *SCD*, sudden cardiac death; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia.

No differences in mortality were observed between men and women in MUSTT (Multicenter Unsustained Tachycardia Trial) [16]. In the electrophysiological guided therapy group, ICD implantation rates were similar in men (45%) and women (53%). The risk of arrhythmic death or cardiac arrest and overall mortality were similar in men and women. In MADIT-II, no specific interaction by sex was observed for the primary outcome [14]. After adjustment for clinical covariates, the survival benefit was similar in men (HR 0.66, 95% CI 0.48−0.91) and women (0.57, 95% CI 0.28−1.18) [17].

DEFINITE reported a mortality benefit of the ICD for prevention of SCD in men (HR 0.49, 95% CI 0.27−0.90, $P = .018$) but not women (HR 1.14, 95% CI 0.50−2.64, $P = .75$, Fig. 77.1) [18]. However, when the interaction for sex and ICD treatment was formally tested using appropriate statistical modeling, a significant interaction between sex and ICD treatment on total mortality was not identified.

Initial subgroup analysis in the Sudden Cardiac Death in Heart Failure Trial suggested that women do not benefit from ICD therapy as much as men compared to placebo therapy (HR 0.96, 95% CI 0.58−1.61 vs. HR 0.73, 95% CI 0.57−0.93) [12]. After adjustment for differences in some baseline characteristics, the mortality risk was lower in women compared with men (HR 0.68, 95% CI 0.55−0.84, $P = .001$) [19]. However, the test for an interaction between sex and ICD treatment was not statistically significant. The DANISH study included 58% of the study population who also received cardiac resynchronization therapy. A sex difference in overall mortality was not observed.

None of the primary prevention trials were powered to compare survival differences between the sexes. Thus, differences in survival outcomes reported should be cautiously interpreted. Registry data have reported that survival in both women and men with reduced left ventricular systolic function is improved by a primary prevention ICD compared to matched controls not receiving this therapy (Fig. 77.2) [20,21].

Arrhythmic events in implantable cardioverter defibrillator recipients

The data from some of the individual randomized clinical trials, metaanalyses of ICD trials [22,23], and data from administrative databases [24−27] have reported that women are less likely to experience treated ventricular arrhythmias following ICD implant. In MADIT-II, the 2-year probability of receiving an appropriate ICD therapy for VT or VF was lower in women (21%) compared with men (28%, $P = .18$, Fig. 77.3). When tested for sex in a multivariate model, women were significantly less likely to receive an appropriate ICD therapy compared with men (HR 0.66, 95% CI 0.37−0.98, $P = .039$) [14,17]. In DEFINITE, women tended to experience fewer ICD shocks for VT or VF compared with men (Fig. 77.4). After adjustment for differences in heart failure functional class, the higher risk of appropriate shocks observed in men was not statistically significant (HR 2.56, 95% CI 0.961−0.682, $P = .60$). In SCD-HeFT, women also tended to be less likely to receive appropriate ICD shocks compared with men [12,19].

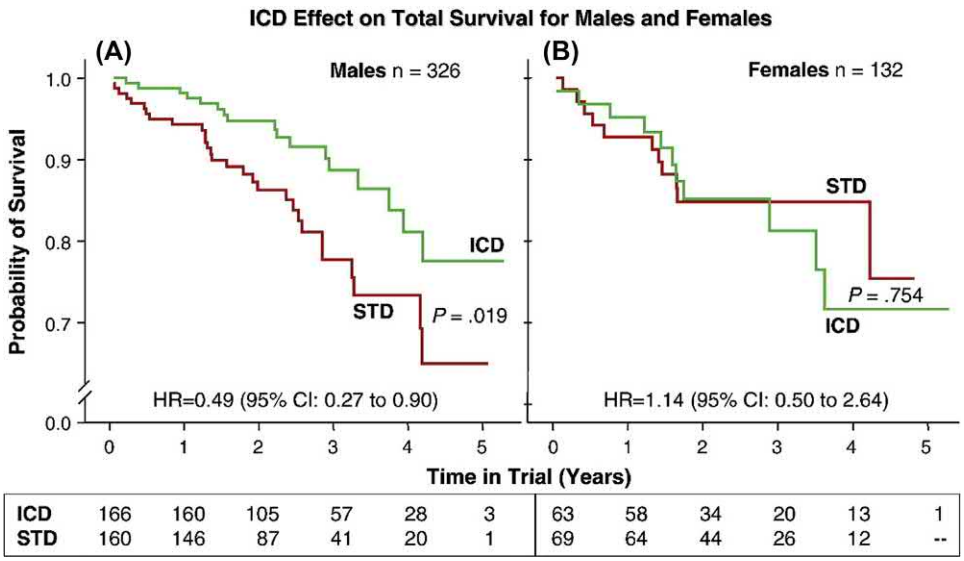


FIGURE 77.1 Sex differences in survival for (A) men and (B) women randomized to implantable cardioverter defibrillator (ICD) versus standard medical therapy in DEFINITE. *Reproduced with permission from Albert CM, Quigg R, Saba S, Estes NA, 3rd, Shaechter A, Subacius H, et al. Sex differences in outcome after implantable cardioverter defibrillator implantation in nonischemic cardiomyopathy. Am Heart J 2008;156(2):367−372.*

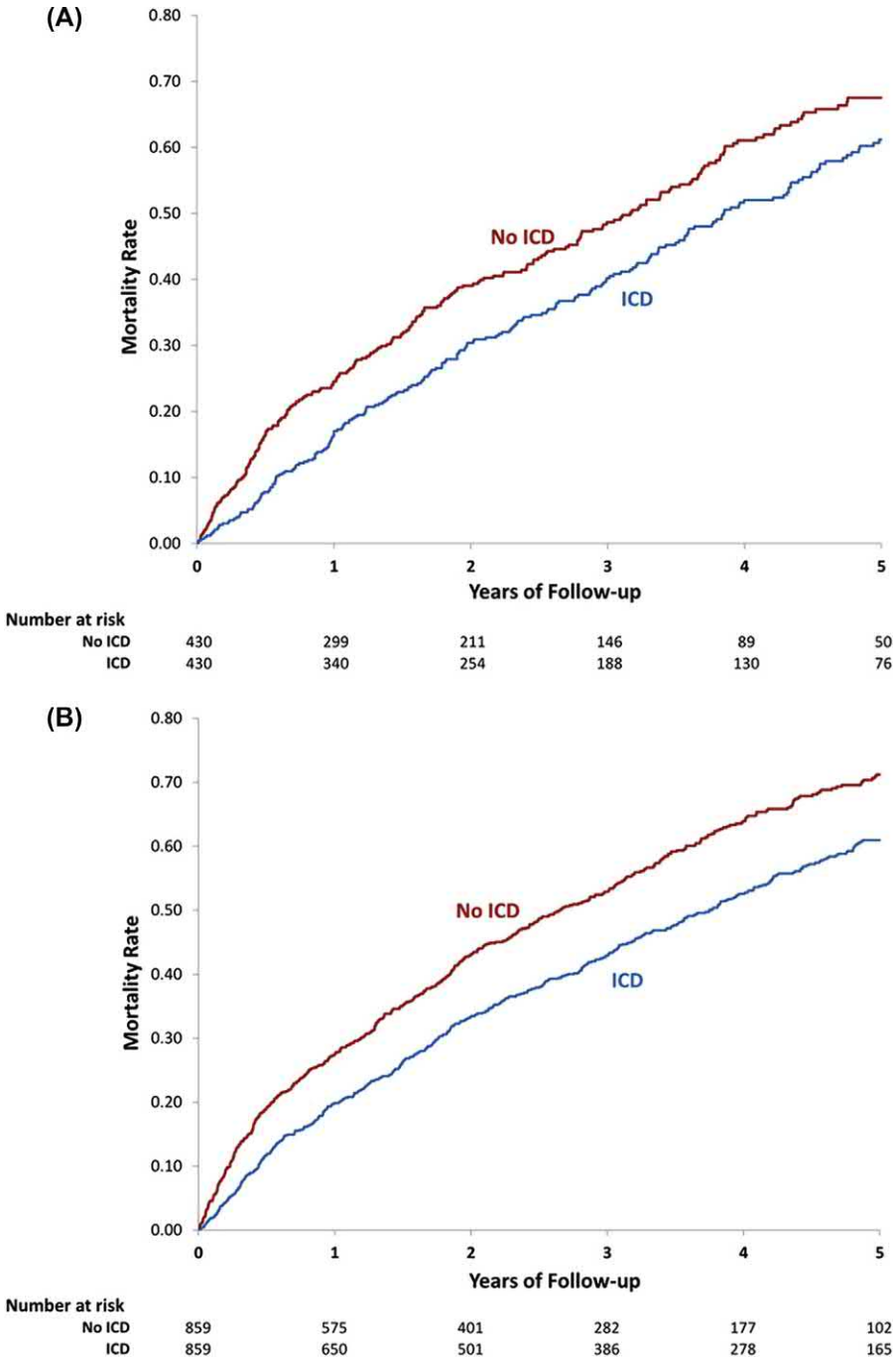


FIGURE 77.2 Survival rates for women (A) and men (B) receiving implantable cardioverter defibrillator (ICD) therapy during or following a heart failure hospitalization compared to a matched cohort not receiving ICD therapy. *Reproduced with permission from Zeitler EP, Hellkamp AS, Schulte PJ, Fonarow GC, Hernandez AF, Peterson ED, et al. Comparative effectiveness of implantable cardioverter defibrillators for primary prevention in women. Circ Heart Fail 2016;9(1):e002630.*

ICD registry data also report that women are less likely to receive appropriate ICD therapies compared with men [24–27]. The Ontario ICD Database—a prospective population-based registry—reported that women were significantly less likely to receive an appropriate ICD shock compared with men (HR 0.69, 95% CI 0.51–0.93, $P = .015$, Fig. 77.5). Rates of inappropriate shocks were similar between men and women. Women were also significantly less likely to receive an appropriate anti-tachycardia pacing therapy for VT compared with men (HR 0.73, 95% CI 0.59–0.90, $P = .003$, Fig. 77.6). These data are reviewed in more detail in Chapter 76.

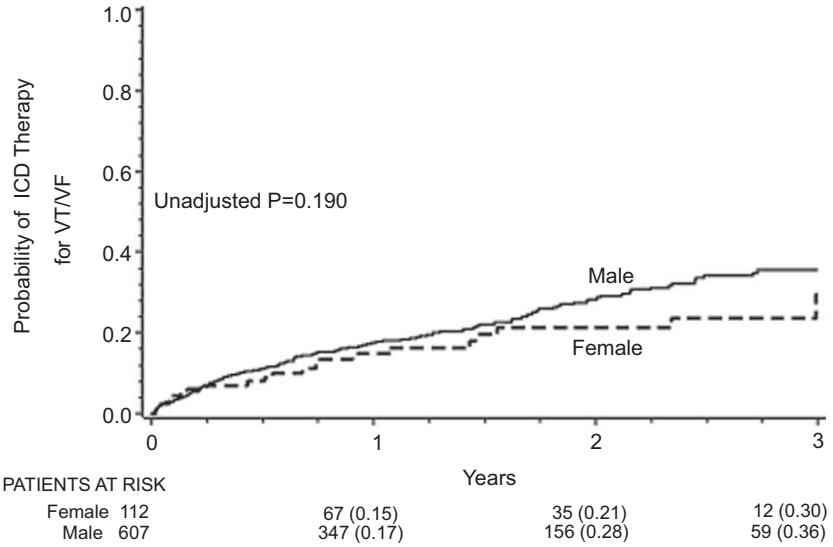


FIGURE 77.3 Sex differences in first appropriate implantable cardioverter defibrillator (ICD) therapy for VT or VF in MADIT-II. *VF*, ventricular fibrillation; *VT*, ventricular tachycardia. *Reproduced with permission from Zareba W, Moss AJ, Jackson Hall W, Wilber DJ, Ruskin JN, McNitt S, et al. Clinical course and implantable cardioverter defibrillator therapy in postinfarction women with severe left ventricular dysfunction. J Cardiovasc Electrophysiol 2005;16(12):1265–1270.*

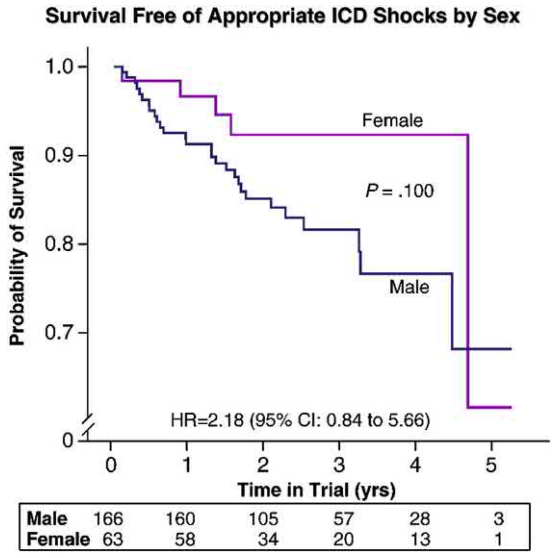


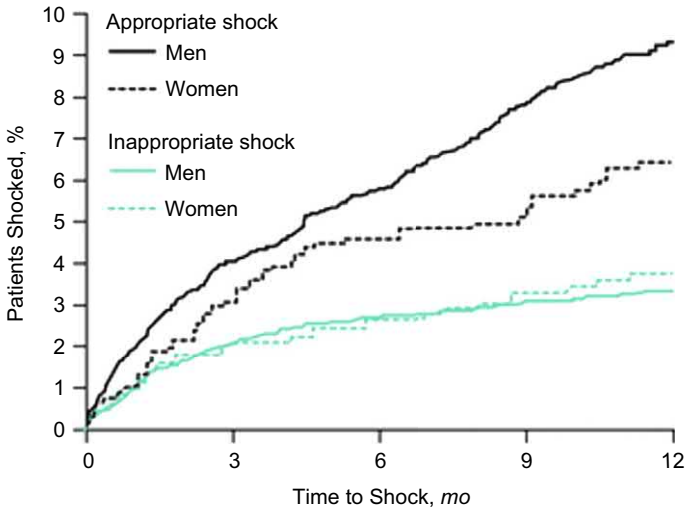
FIGURE 77.4 Sex differences in appropriate implantable cardioverter defibrillator (ICD) shocks in DEFINITE. *Reproduced with permission from Albert CM, Quigg R, Saba S, Estes NA, 3rd, Shaechter A, Subacius H, et al. Sex differences in outcome after implantable cardioverter defibrillator implantation in nonischemic cardiomyopathy. Am Heart J 2008;156(2):367–372.*

The MADIT-CRT investigators reported a detailed analysis of sex differences in VT/VF events [28]. Over 3 years of follow-up, fewer women (21%) experienced VT/VF or death compared with men (35%, $P < .001$). The mean number of treated ventricular arrhythmia episodes was significantly lower in women compared with men (VT 0.60 ± 3.0 vs. 1.97 ± 12.2, $P < .0001$; VF 0.12 ± 0.83 vs. 0.24 ± 3.0, $P = .033$). Overall women were 38% less likely to experience VT/VF or death compared with men. The cumulative incidence of VT/VF or death based on sex and etiology of heart disease is illustrated in Fig. 77.7. The probability of VT/VF or death was significantly lower in women compared with men with ischemic heart disease. For those with nonischemic heart disease, the cumulative probability of VT/VF or death is similar. Independent of the underlying etiology of heart disease (ischemic or nonischemic), the cumulative incidence of VT/VF (Fig. 77.7 right panel) was significantly lower in women compared with men.

Recently, the RAFT investigators reported sex differences in outcomes of patients randomized to CRT-ICD versus ICD therapy [29]. Compared with men, women tended to be less likely to experience a ventricular arrhythmia. Women receiving CRT-ICD for a primary prevention indication had the lowest rate of ventricular arrhythmia compared with men (HR 0.59, 95% CI 0.39–0.91, $P = .016$, Fig. 77.8).

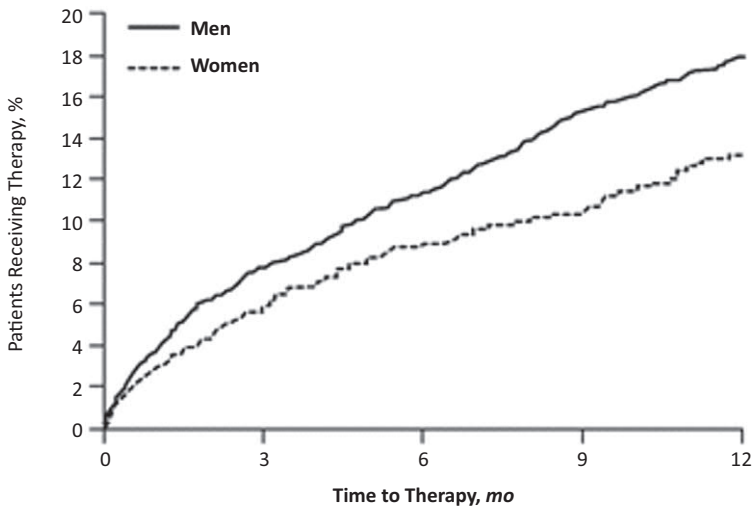
In MADIT-CRT, women were less likely to receive an inappropriate ICD therapy or ICD shock compared with men [30]. Women receiving a CRT-ICD experienced fewer inappropriate shocks compared with women receiving an ICD. In contrast, inappropriate ICD shock rates have been reported to be similar in both men and women followed in the Ontario ICD registry [24] and in a multicenter European Registry [25].

The reasons for the sex differences in ventricular arrhythmia event rates are not completely understood. Differences in arrhythmia substrate may be important, as



At risk for appropriate shock, *n*					
Men	4108	3478	2997	2578	2222
Women	1105	943	825	724	639
At risk for inappropriate shock, *n*					
Men	4108	3550	3091	2718	2365
Women	1105	950	833	736	653

FIGURE 77.5 Sex differences in appropriate and inappropriate implantable cardioverter defibrillator (ICD) therapies in patients followed in the Ontario ICD Database. *Reproduced with permission from MacFadden DR, Crystal E, Krahn AD, Mangat I, Healey JS, Dorian P, et al. Sex differences in implantable cardioverter-defibrillator outcomes: findings from a prospective defibrillator database. Ann Intern Med 2012;156(3):195–203.*



At risk for appropriate therapy, *n*					
Men	4108	3350	2826	2388	2011
Women	1105	919	790	688	595

FIGURE 77.6 Sex differences in time to first appropriate antitachycardia pacing therapy for VT in patients followed in the Ontario ICD Database. *VT*, ventricular tachycardia. *Reproduced with permission from MacFadden DR, Crystal E, Krahn AD, Mangat I, Healey JS, Dorian P, et al. Sex differences in implantable cardioverter-defibrillator outcomes: findings from a prospective defibrillator database. Ann Intern Med 2012;156(3):195–203.*

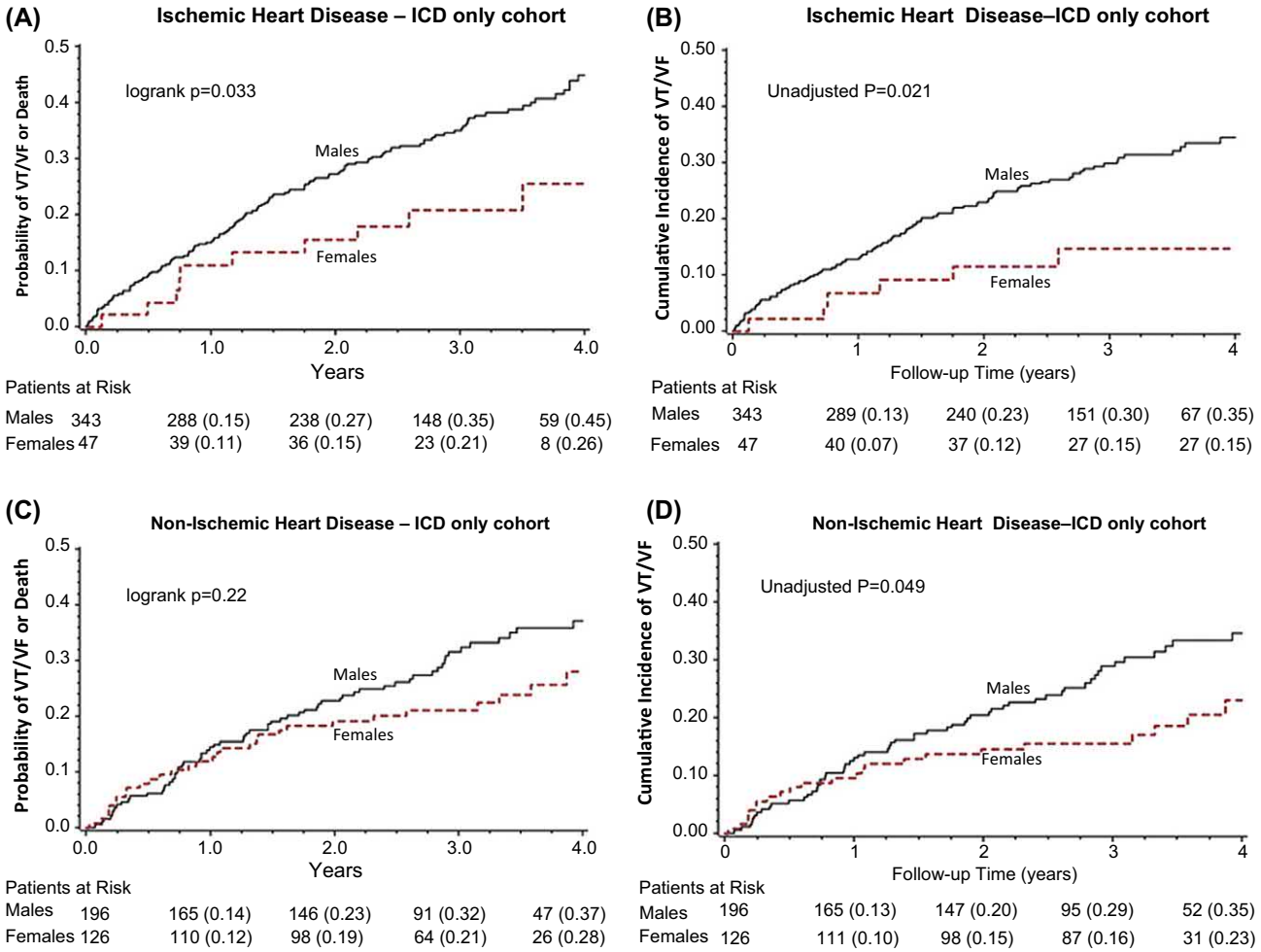


FIGURE 77.7 Sex differences in VT/VF in MADIT-CRT. Left panels: Cumulative probability of VT/VF or death based on sex or etiology of heart disease. Right panels: Cumulative probability of VT or VF based on sex and etiology of heart disease. Women were less likely to experience VT or VF independent of type of heart disease. *VF*, ventricular fibrillation; *VT*, ventricular tachycardia. *Reproduced with permission from Tompkins CM, Kutyifa V, Arshad A, McNitt S, Polonsky B, Wang PJ, et al. Sex differences in device therapies for ventricular arrhythmias or death in the multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy (MADIT-CRT) trial. J Cardiovasc Electrophysiol 2015;26(8):862–871.*

men are more likely to have ischemic heart disease and scar-related VT compared with women [31]. Sex differences in ion channel expression/function, autonomic regulation, and differences in intracellular calcium handling may also influence the substrate and triggers for ventricular arrhythmias [32,33].

Sex differences in implantable cardioverter defibrillator–related complications

Several studies have reported that women experience more ICD-related complications compared with men [24,34–37]. Data from the NCDR ICD Registry reported that women are more likely to experience any adverse event (4.4% vs. 3.3% $P < .001$) or a major adverse event (2.0% vs. 1.1%, $P < .001$, Fig. 77.9) compared with men [34]. Women experienced a higher rate of pneumothorax, hematoma requiring transfusion or evacuation, cardiac perforation/tamponade, and hemothorax [34,35]. Women were also more likely to experience lead dislodgement. After adjustment for a number of baseline characteristics, this sex difference in risk of adverse events remained (OR 1.71, 95% CI 1.57–1.86, for a major adverse event). The sex difference in risk of any adverse event was greatest in those ≥65 years. Other registry studies have confirmed the higher risk of device-related complications in women compared with men including higher complication rates in women during long-term follow-up [24,35].

Sex differences in implantable cardioverter defibrillator utilization

The pivotal randomized clinical trials led to the development of clinical practice guidelines recommending the implantation of an ICD for primary and secondary prevention of SCD in high-risk populations [38]. However,

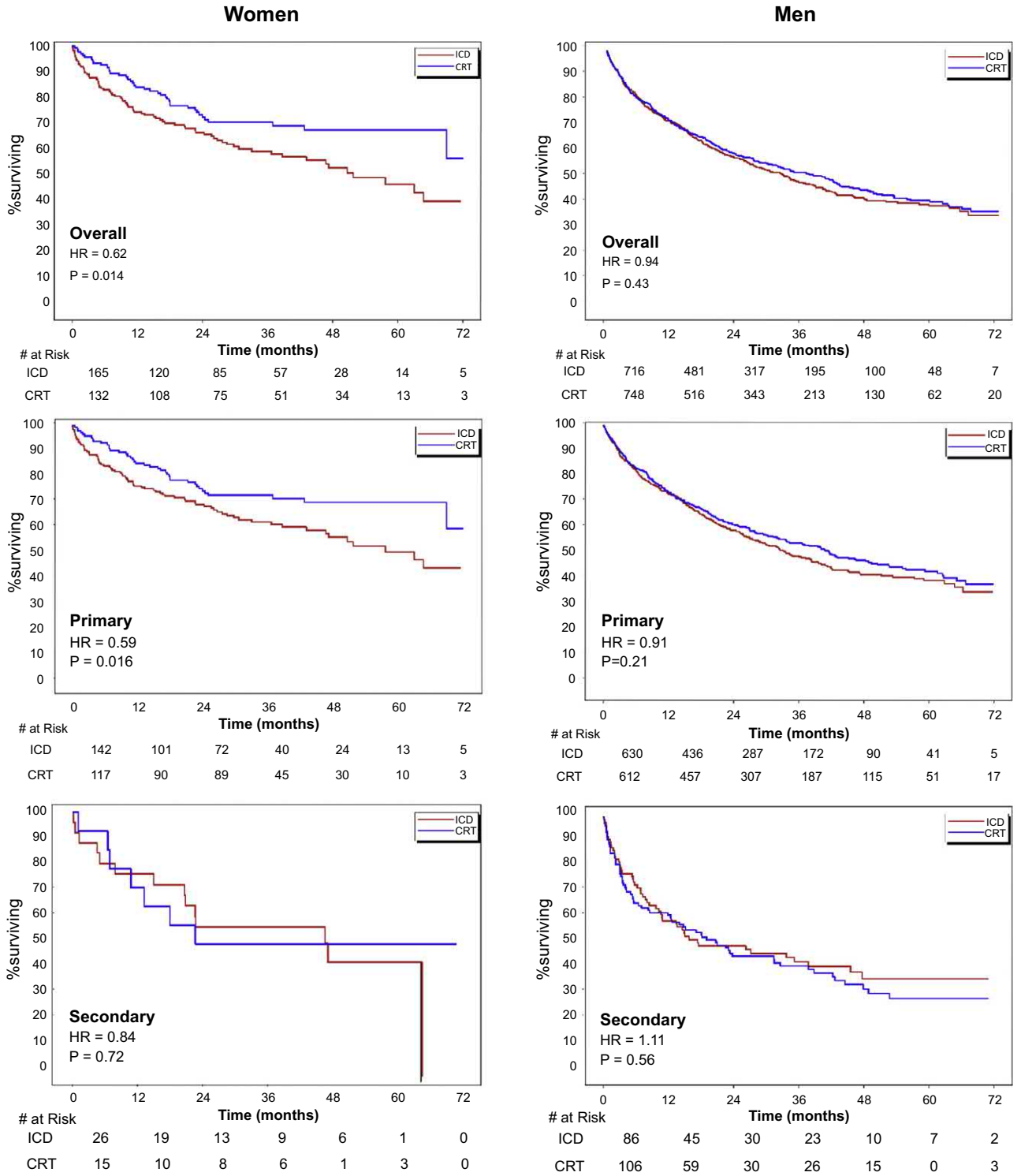


FIGURE 77.8 Time to ventricular arrhythmia events treated in RAFT based on sex and randomized device therapy. Upper Panels: Entire cohort; Middle Panels: Primary Prevention Cohort; Lower Panels: Secondary Prevention Cohort. *Reproduced with permission from de Waard D, Manlucu J, Gillis AM, Sapp J, Bernick J, Doucette S, et al. Cardiac resynchronization in women: a substudy of the resynchronization-defibrillation for ambulatory heart failure trial. JACC Clin Electrophysiol 2019;5(9):1036–1044.*

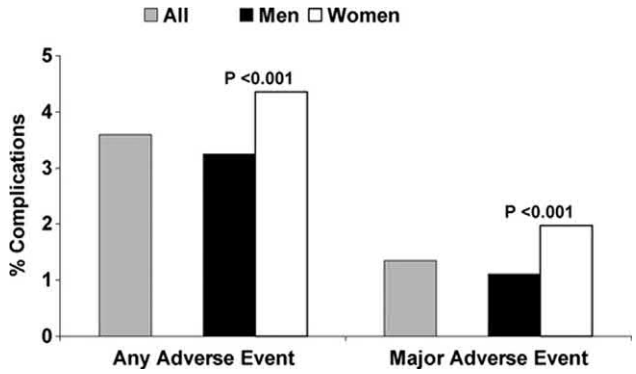
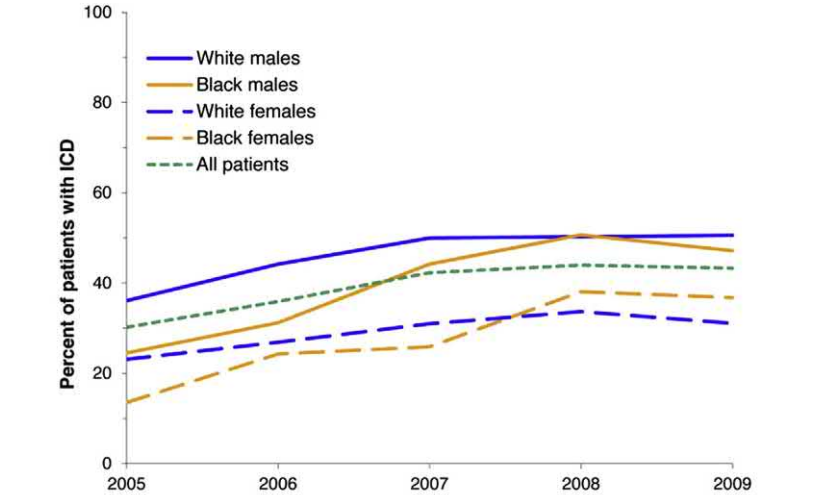


FIGURE 77.9 Sex differences in implantable cardioverter defibrillator–related complications. Rates of any adverse event and major adverse events in the total population, men, and women are shown. *Reproduced with permission from Peterson PN, Daugherty SL, Wang Y, Vidaillet HJ, Heidenreich PA, Curtis JP, et al. Gender differences in procedure-related adverse events in patients receiving implantable cardioverter-defibrillator therapy. Circulation 2009;119(8):1078–1084.*

multiple studies have reported that women are less likely to receive an ICD for primary and secondary prevention indications [39–42], although this gap appears to be narrowing over time [24,43]. Curtis et al. analyzed a Medicare sample including those ≥65 years of age with a diagnosis of prior myocardial infarction or cardiomyopathy and heart failure (primary prevention cohort) and patients presenting with a cardiac arrest or sustained VT (secondary prevention cohort) [39]. After controlling for differences in baseline characteristics in the primary prevention cohort, men were more likely than women to receive ICD therapy (HR 3.15; 95% CI 2.86–3.47). In the secondary prevention cohort, men also were more likely than women to receive ICD therapy (HR, 2.44; 95% CI, 2.30–2.59). Of those receiving a secondary prevention ICD, the mortality benefit was significant for both women (HR, 0.68; 95% CI, 0.60–0.78) and men (HR, 0.62; 95% CI, 0.55–0.69) [39].

Sex disparities in ICD utilization for both primary and secondary prevention of SCD have also been reported in a Canadian population cohort of patients hospitalized in the province of Ontario [40]. Men presenting with a cardiac arrest were more likely to undergo ICD implantation compared with women (HR 1.92, 95% CI 1.66–2.23). Men presenting with a primary prevention indication following myocardial infarction were threefold more likely to undergo ICD implantation compared with women (adjusted HR 3.00, 95% CI: 2.53–3.55). In addition, men with a diagnosis of heart failure and associated left ventricular systolic dysfunction were threefold more likely to undergo ICD implantation compared with women (adjusted HR 3.01, 95% CI 2.59–3.50). The odds of ICD implant for secondary prevention increased over time by 21% in women and by 6% in men. However, ICD implant rates remained persistently higher in men for primary prevention indications. Age and relevant comorbidities did not explain the sex disparities in ICD utilization noted in this cohort.

Of patients with heart failure and a reduced LVEF discharged from hospitals participating in the Get With The Guidelines-Heart Failure, the rates of ICD implantation were lower among eligible women and black patients compared with white men [44]. A more recent analysis of patients with heart failure enrolled in this program reported that ICD utilization rates have increased over time [43]. Although the racial disparities previously reported have improved, the sex differences have persisted (Fig. 77.10).



Number of patients						Total
White males	856	1304	1189	1403	1268	6020
Black males	106	157	197	223	195	878
White females	480	699	606	744	647	3176
Black females	89	144	170	181	155	739
All patients	1671	2499	2368	2822	2520	11880

FIGURE 77.10 Temporal changes in implantable cardioverter defibrillator (ICD) use in the overall study population and in sex and race groups. Temporal trend *P* values < .0001 overall and for each of the four sex and race groups. *Reproduced with permission from Al-Khatib SM, Hellkamp AS, Hernandez AF, Fonarow GC, Thomas KL, Al-Khalidi HR, et al. Trends in use of implantable cardioverter-defibrillator therapy among patients hospitalized for heart failure: have the previously observed sex and racial disparities changed over time? Circulation 2012;125(9):1094–1101.*

Subsequent analysis of this cohort reports that women with heart failure and left ventricular dysfunction were significantly less likely to receive counseling about ICD therapy compared with men (19% vs. 25%, $P < .001$). However, of those patients receiving counseling, subsequent ICD implantation rates were similar for both men and women [45]. Analysis of an Ontario prospective ICD database confirms that ICD implantation rates were similar for men and women after referral to an electrophysiologist [24].

The reasons for the sex disparity in ICD utilization are not completely understood and are likely multifactorial [42,46]. It is possible that women who were underrepresented in the pivotal randomized trials are less likely to be referred for ICD therapy because of the perception of less benefit. It is also possible that preferences and perceptions of therapy differ between the sexes.

Summary

The ICD improves survival in patients with indications for primary and secondary prevention of sudden death. Women were underrepresented in the clinical trials demonstrating this benefit and the studies were not adequately powered to assess a potential sex difference in benefit from ICD therapy. Data from multiple studies report that women are less likely to experience VT/VF episodes following ICD implantation. This sex difference in ventricular arrhythmia incidence and rates likely reflects differences in the underlying causes of heart disease and arrhythmia substrate. Nevertheless, current data support a survival benefit of ICD therapy in women at risk for SCD that is reflected in current guidelines.

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Chapter 78

ICD registries and sex-specific metanalyses

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Abbreviations

CI confidence interval
CMS Centers for Medicare and Medicaid Services
COPD chronic obstructive pulmonary disease
CRT-D cardiac resynchronization therapy with defibrillator
eGFR estimated glomerular filtration rate
EU-CERT-ICD Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators in Europe
GWTG-HF Get With The Guidelines—Heart Failure
HR hazard ratio
ICD implantable cardioverter defibrillator
LVEF left ventricular ejection fraction
NCDR National Cardiovascular Data Registry
NYHA New York Heart Association
SCD sudden cardiac death
SCD-HeFT Sudden Cardiac Death in Heart Failure Trial
vs versus
WP work package

Introduction

Implantable cardioverter defibrillators (ICDs) are an established first-line therapy in patients with cardiovascular disease who are at increased risk of sudden cardiac death (SCD) [1–6]. However, a considerable number of patients never receive appropriate therapy and thus, on an individual basis, have not derived benefit. In addition to a lower all-cause and arrhythmic mortality, this may be explained with a high risk of nonarrhythmic death competing with the risk of shock in ICD patients [7].

Current guidelines apply to both women and men without differentiation. Notwithstanding, controversial results have been reported in the literature regarding a smaller ICD mortality benefit for women. Although not a prespecified subgroup, a smaller treatment benefit for women was already seen in the original SCD-HeFT publication [6]. Subsequent secondary publications from the major ICD studies showed similar sex-related differences in the treatment benefit of the ICD but discarded significance noting that sex did not interact statistically with ICD benefit [8]. As women typically contribute only between 15% and 25% of the studies' patient number, the lack of statistical interaction may well be due to underpowering. As will be described in this chapter on sex-related results of ICD registries and ICD metaanalyses, sex differences in outcomes can be reproducibly detected. It remains difficult to translate these into significant consequences when selecting patients for ICD implantation. As a result, further studies in this important subgroup of ICD patients are clearly warranted.

Sex differences of implantable cardioverter defibrillator outcomes in registries

Ontario ICD registry

MacFadden et al. [9] published important data from the Ontario registry regarding the question of potential sex differences in ICD device outcomes and implantation numbers. The Ontario ICD registry was launched in all 18 ICD implanting centers of the Canadian province of Ontario (population c. 13 million) [10]. All consecutive ICD implantations were entered in a web-based registry between 2007 and 2011; funding was provided by the Ontario Ministry of Health and the Canadian Institutes of Health Research. The purpose was to prospectively collect characteristics and outcomes of all patients undergoing ICD device implantations. In addition to all-cause mortality, this included follow-up hospitalizations, early or late ICD

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complications, and device follow-up for ICD therapies and shocks. Last follow-ups were done in 2012. Another primary aim of the Ontario ICD registry was to develop risk stratification strategies [11], as applied for the female patients. Among the 5213 patients enrolled, there were 1105 women (21%). As one of the major findings from this registry, female patients were 31% less likely to experience an appropriate ICD shock (HR [hazard ratio]: 0.69; CI [confidence interval]: 0.51−0.93; $P = .015$). A very similar result was found when considering appropriate ICD therapies via shock or antitachycardia pacing (HR: 0.73; CI: 0.59−0.90; $P = .003$). In contrast, total mortality among defibrillator recipients did not differ between men and women (HR: 1.00; CI: 0.64−1.55; $P = .99$).

Single-center Göttingen ICD registry

In a retrospective single-center study at University Medical Center Göttingen by Seegers et al. [12], 1151 consecutive patients undergoing ICD or cardiac resynchronization therapy with defibrillator (CRT-D) between 1998 and 2010 were analyzed for mortality and first appropriate ICD shock. The series included 216 women (19%). The aim was to further investigate sex differences in a large single-center population with long-term follow-up. Baseline characteristics available included age, sex, body mass index, systolic blood pressure, ischemic or nonischemic disease, primary or secondary prophylactic defibrillator indication, New York Heart Association (NYHA) functional class, echocardiographic left ventricular ejection fraction (LVEF), cardiovascular drug treatment, and comorbidities. Serum creatinine at implantation was used to calculate the estimated glomerular filtration rate (eGFR). Underlying rhythm, heart rate, QRS, and uncorrected QT duration were measured from the electrocardiogram. The cohort was typical for ICD patients with an average age of 64 ± 13 years, LVEF of 31 ± 12%, 65% with ischemic cardiomyopathy, 54% with a primary prophylactic indication, 34% with CRT-Ds, NYHA functional class of 2.4 ± 0.9, and an eGFR of 67 ± 25 mL/min/m^2. Over a considerable long-term follow-up of 4.9 ± 2.7 years (the maximum was 14.0 years), 318 patients died translating into an unadjusted annualized rate of 5.9% per year for men and 4.6% for women ($P = .08$); 266 patients received a first appropriate ICD shock (6.3% per year for men vs. 3.6% for women, $P = .002$). Only 84 (26.4%) of the 318 deceased patients received at least one appropriate ICD shock, 234 patients (73.6%) died without prior appropriate shock. Sex-related differences were studied by means of univariable and multivariable Cox regression models. Sex category was entered into all multivariate models regardless of *P*-value. Death was regarded as a competing risk for appropriate ICD shocks [13]. When correcting by means of a multivariate Cox model, sex category did not turn out as an independent predictor of all-cause death. Univariate and multivariate Cox proportional hazards regression for all-cause mortality are shown in Table 78.1A. Univariate Cox regression showed a number of typical predictors for mortality, with only a nonsignificant trend for better survival of women versus men. Age, LVEF, eGFR, diuretics, aspirin, peripheral arterial disease, and chronic obstructive pulmonary disease (COPD) were selected as independent predictors of all-cause mortality in the final Cox model. Sex was not a predictor of mortality in the multivariable model (HR: 1.15; 95% CI: 0.84−1.58; $P = .536$). Univariate and multivariate Fine−Gray competing risk regression for first appropriate shock is shown in Table 78.1B. Univariate Cox regression revealed a significant association of first appropriate shock with male sex, secondary prophylactic ICD indication, prolonged QT interval, oral anticoagulation, treatment with amiodarone, history of atrial fibrillation, and COPD. Women were subject to significantly less appropriate ICD shocks (3.6% as compared with 6.3% per year, $P = .002$, Fig. 78.1). After adjustment in the final multivariate Cox model, higher age (HR: 0.98; 95% CI: 0.97−0.99; $P < .001$), female sex (HR: 0.51; 95% CI: 0.33−0.81; $P = .013$), and primary prophylactic indication (HR: 0.69; 95% CI:0.52−0.93; $P = .043$) were identified as independent predictors of fewer appropriate ICD shocks (Table 78.1B). When differentiating primary and secondary prophylactic ICD therapy patients, the uncorrected shock rate was significantly lower in women in both groups (2.6% vs. 4.8% per year, $P = .033$, and 4.9 vs. 7.4% per year, $P = .018$, respectively). Inappropriate shocks were equally distributed between men and women (9.5 vs. 7.9%, $P = .45$).

Other single-center ICD registries

Single-center registry data on the risks of women versus men as ICD recipients were also published by van der Heijden et al. [14] and provided very similar results in 1946 ICD patients including 418 women (21%). Again, after adjustment for cofactors, women were less likely to experience appropriate shock (HR: 0.82; 95% CI: 0.64−1.06; $P = .13$). Similarly, Wijers et al. [15] in 1075 patients including 279 women (26%) reported an HR of 0.43 (95% CI: 0.26−0.71, $P = .001$) for appropriate shock in women after multivariate correction. In both studies, women also exhibited a lower all-cause mortality (HR: 0.65; 95% CI: 0.49−0.84; $P < .01$and HR: 0.53; 95% CI: 0.33−0.77; $P = .004$).

Rationale of conducting additional sex difference studies in the EU-CERT-ICD project

To summarize the aforementioned, the ICD population from the University Medical Center in Göttingen [12]

TABLE 78.1A Univariate and multivariate Cox proportional hazards regression (final model) for all-cause mortality.

	Univariate		Multivariate	
	HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
Age (years)	1.058 [1.046–1.071]	**<0.001**	1.04 [1.03–1.06]	**<0.001**
Sex category (male)	1.302 [0.960–1.766]	0.090	1.15 [0.84–1.58]	0.536
Body mass index (kg/m^2)	0.977 [0.951–1.003]	0.082		
NYHA functional class	1.587 [1.385–1.819]	**<0.001**		
Primary prophylactic indication	1.444 [1.150–1.815]	**0.002**		
CRT-D	1.515 [1.212–1.893]	**<0.001**		
Ischemic cardiomyopathy	1.501 [1.166–1.932]	**0.002**		
LVEF (%)	0.972 [0.962–0.983]	**<0.001**	0.98 [0.97–1.00]	**0.025**
Heart rate (b.p.m.)	1.002 [0.998–1.005]	0.336		
QRS duration (ms)	1.007 [1.004–1.011]	**<0.001**		
QT interval (ms)	1.003 [1.000–1.005]	**0.027**		
eGFR (mL/min/1.73 m^2)	0.979 [0.974–0.984]	**<0.001**	0.99 [0.99–1.00]	**0.009**
Medication				
ACE inhibitors/ARB	0.997 [0.716–1.388]	0.986		
β-Blocker	0.923 [0.651–1.309]	0.654		
Digitalis	1.507 [1.197–1.898]	**<0.001**		
Diuretics	2.872 [2.058–4.008]	**<0.001**	1.81 [1.29–2.54]	**0.002**
MRA	1.012 [0.805–1.273]	0.918		
Aspirin	0.996 [0.792–1.251]	0.971	0.73 [0.58–0.93]	**0.029**
Coumadin	1.305 [1.025–1.661]	**0.031**		
Amiodarone	1.308 [1.016–1.683]	**0.037**		
Hypertension	1.268 [0.940–1.712]	0.120		
Diabetes	1.587 [1.259–2.001]	**<0.001**		
History of atrial fibrillation	1.546 [1.240–1.928]	**<0.001**		
Peripheral arterial disease	2.874 [2.149–3.843]	**<0.001**	2.21 [1.62–3.00]	**<0.001**
COPD	1.982 [1.520–2.584]	**<0.001**	1.48 [1.13–1.94]	**0.029**

AAD, antiarrhythmic drug; *AF*, atrial fibrillation; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *aspirin*, acetylsalicylic acid; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *CRT-D*, cardiac resynchronization therapy with defibrillator; *eGFR*, estimated glomerular filtration rate; *HR*, hazard ratio; *LVEF*, left ventricular ejection fraction; *MRA*, mineralocorticoid receptor antagonist; *NYHA*, New York Heart Association). Bold denotes significant P-values.
From Seegers J, Conen D, Jung K, Bergau L, Dorenkamp M, Luthje L, et al. Sex difference in appropriate shocks but not mortality during long-term follow-up in patients with implantable cardioverter-defibrillators. Europace. 2016;18(8):1194–1202 with permission.

revealed typical independent predictors of mortality and three independent predictors of appropriate shock during extended follow-up including sex category. In a large single-center cohort, female sex was associated with a ≈50% reduced risk of appropriate shocks after adjustment but did not influence mortality. The important finding reported by the Ontario ICD registry that women had a significantly reduced risk of appropriate ICD shocks was fully confirmed. These results also demonstrated that risk factors for mortality do not correspond with risk factors for malignant ventricular arrhythmias. Interestingly, age was associated not only with an increased mortality but also with a risk reduction in appropriate shocks (HR: 0.98 per year of age; 95% CI: 0.97–0.99; $P < .001$). The paradoxical effect of age on the incidence of appropriate shocks was also reported in almost the same size by the Ontario registry (HR: 0.82 per 10 years of age; 95% CI: 0.72–0.94; $P = .004$) [11]. This finding could further limit the benefit

TABLE 78.1B Univariate and multivariate Cox proportional hazards regression (final model) for occurrence of the first appropriate shock.

	Univariate		Multivariate	
	HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
Age (years)	0.999 [0.990–1.008]	0.838	0.98 [0.97–0.99]	**<0.001**
Sex category (male)	1.773 [1.225–2.567]	**0.002**	1.94 [1.23–3.04]	**0.013**
Body mass index (kg/m^2)	1.001 [0.975–1.027]	0.968		
NYHA functional class	0.944 [0.823–1.083]	0.411		
Primary prophylactic indication	0.655 [0.512–0.838]	**0.001**	0.69 [0.52–0.93]	**0.043**
CRT-D	0.969 [0.751–1.249]	0.806		
Ischemic cardiomyopathy	1.102 [0.850–1.428]	0.465		
LVEF (%)	0.995 [0.985–1.006]	0.358		
Heart rate (b.p.m.)	0.992 [0.985–1.001]	0.068		
QRS duration (ms)	0.999 [0.995–1.003]	0.734		
QT interval (ms)	1.003 [1.001–1.006]	**0.013**		
eGFR (mL/min/1.73 m^2)	0.998 [0.993–1.004]	0.546		
Medication				
ACE inhibitors/ARB	1.048 [0.722–1.519]	0.807		
jS-Blocker	0.901 [0.609–1.334]	0.603		
Digitalis	1.019 [0.781–1.330]	0.889		
Diuretics	1.096 [0.831–1.445]	0.515		
MRA	0.959 [0.749–1.228]	0.739		
Aspirin	0.788 [0.616–1.007]	0.057		
Coumadin	1.391 [1.072–1.804]	**0.013**		
Amiodarone	1.900 [1.460–2.474]	**<0.001**		
Hypertension	1.010 [0.741–1.377]	0.950		
Diabetes	1.008 [0.765–1.328]	0.953		
History of atrial fibrillation	1.335 [1.047–1.701]	**0.020**		
Peripheral arterial disease	0.901 [0.565–1.437]	0.661		
COPD	1.385 [1.010–1.900]	**0.043**		

AAD, antiarrhythmic drug; *AF*, atrial fibrillation; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *aspirin*, acetylsalicylic acid; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *CRT-D*, cardiac resynchronization therapy with defibrillator; *eGFR*, estimated glomerular filtration rate; *HR*, hazard ratio; *LVEF*, left ventricular ejection fraction; *MRA*, mineralocorticoid receptor antagonist; *NYHA*, New York Heart Association.

of ICDs in the elderly. One could again hypothesize here that women derive a smaller benefit from their device if they exhibit less malignant ventricular arrhythmias and mortality is similar after multivariate correction. This would not contradict ICD therapy in women but could support a strategy that individually a higher threshold for an ICD indication could be warranted for women. In their 2013 article [16], Goldberger and Buxton have called for personalized decisions on guideline-recommended indications using patient characteristics, a concept that could potentially be applied to the clinical decision of an ICD indication. This could pertain to the level of left ventricular dysfunction in primary prophylactic indications or the presence of additional risk factors. Increased risk for ICD-associated complications may further decrease benefit from the device among women [9,17] but was not assessed in this study. How sex differences translate into clinical arrhythmias and possibly appropriate ICD shocks is not fully clear. This

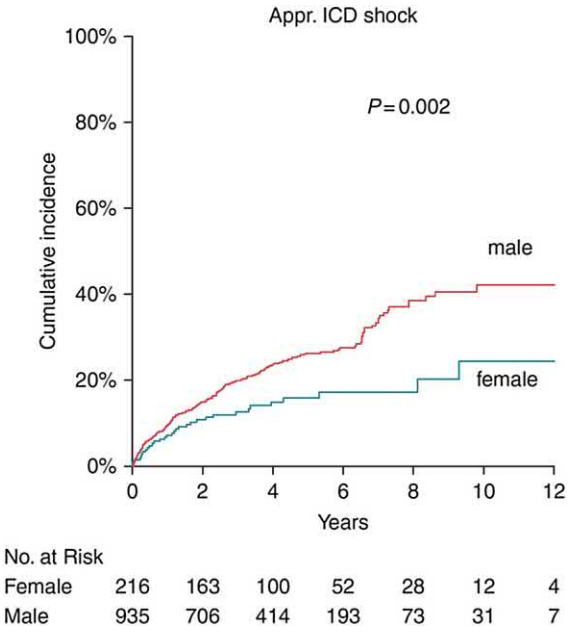

FIGURE 78.1 Cumulative Kaplan–Meier event probability of first appropriate ICD shock in the single-center Göttingen registry: male (*red line*) and female (*blue line*) patients. Unadjusted *P*-value is shown in the figure. *ICD*, implantable cardioverter defibrillator. *From Seegers J, Conen D, Jung K, Bergau L, Dorenkamp M, Luthje L, et al. Sex difference in appropriate shocks but not mortality during long-term follow-up in patients with implantable cardioverter-defibrillators. Europace. 2016;18(8):1194–1202 with permission.*

is the subject of multiple chapters in this book. More data and insights to evaluate the risks and benefits of ICD therapy for primary prevention with a focus on sex were clearly necessary and to be generated in the retrospective EU-CERT-ICD (Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators in Europe) registry [18] in over 5300 patients and the prospective EU-CERT-ICD study in 2327 patients. The results of the EU-CERT-ICD retrospective registry are described here.

The European Cooperative Seventh Framework Programme project EU-CERT-ICD was funded as a modular research project from 2013 to 2018 to study the effectiveness of prophylactic ICD treatment. In addition to the large prospective study [19] (www.eu-cert-icd.eu, NCT02064192), retrospective studies [12,18] and meta-analyses in primary prophylactic ICD patients were part of the funded project [20,21]. The sample size of the prospective study was also powered for sex category–specific issues. Several manuscripts [12,19,22–33] have been published from the various work packages; the prospective study [19] has completed its follow-up and is currently being analyzed. Prospectively, the EU-CERT-ICD non-randomized controlled study will specifically look at the benefit of ICD therapy versus control in women, and these results should become available shortly [19]. A non-randomized design was chosen because the generation of specific randomized ICD data in primary prophylactic patients, and women in particular, was deemed ethically problematic at the outset of the study. This may still be the case. As the percentage of women among ICD candidates is typically around 20%, huge numbers of ICD patients would have to be screened before enrollment. In the prospective study, 2327 patients were enrolled in two parallel nonrandomized patient groups. More than 1500 patients were recruited at first prophylactic ICD implantation, whereas more than 750 patients were non-ICD control patients who had an indication for ICD therapy with an LVEF $\leq$35% and ischemic or dilated cardiomyopathies. The majority of the latter patients were enrolled from European countries where prophylactic ICD therapy was not available (Bulgaria, Croatia, Denmark/patients with dilated cardiomyopathy) or patients had refused implantation of an indicated ICD. Importantly, the EU-CERT-ICD project also featured a retrospective registry work package (WP02) with the collection of more than 5300 cases from 14 participants. Thus, within this framework, the prospective study, registries, and metaanalyses were aiming to look further at the relative risks and benefits of women in large groups of ICD patients.

Sex differences in outcomes in the EU-CERT-ICD multicenter registry

The EU-CERT-ICD combined ICD registry [18] aimed to determine the effectiveness of primary prevention ICD therapy by analyzing registry data from 11 European countries. Emphasis was put on outcomes of women based on the previously described rationale. Retrospective data of 14 local registries were compiled in a new database as WP02 of the project. First ICD implantations between 2002 and 2014 were included. Predefined outcomes of both the prospective and retrospective studies were all-cause mortality and appropriate ICD shock. By means of a multivariable statistical model, a common HR for sex category across all centers was calculated (it also allowed for center-specific effects) and adjusted for age, ischemic cardiomyopathy, LVEF<25%, and cardiac resynchronization therapy ICD (CRT-D). An interaction term for sex category and CRT-D interactions was specifically added to the models. Data from 5111 patients were available. Excluding 78 patients with incomplete follow-up, 5033 patients were analyzable for mortality. Of these, 957 (19%) were women. Mean age at implantation was 64 $\pm$ 11 years, 65% had ischemic cardiomyopathy, and 43% were implanted a CRT-D. Median follow-up was 33 months, during which 936 patients died. All-cause mortality was significantly lower for women (129 deaths; 13%) than for men (807 deaths; 20%); of these, 95 females (11%) and 584

males (16%) died before receiving an appropriate shock, and another 13 females (2%) and 50 males (1%) underwent heart transplantation prior to any appropriate shock. For the analysis of first appropriate shock, data from 4548 patients were available, from which 139 patients had to be excluded as incomplete. During a median follow-up of 29 months, 566 patients had at least one appropriate shock (65 females and 501 males). The estimated cumulative incidence curves and their 95% CI showed a significantly lower number of first appropriate ICD shocks for women (Fig. 78.2). As the endpoint of first appropriate shock competed with endpoints of death and heart transplantation, for multivariate analyses, a competing risk regression analysis as proposed by Fine and Gray was required [13]. The HR for sex category adjusted for age, ischemic cardiomyopathy, LVEF $\leq$25%, and CRT-D was 0.61 (95% CI: 0.47−0.80; $P = .0003$). Analysis of individual centers showed no evidence for heterogeneity ($I^2 = 0$, heterogeneity test $P = .8788$), and the pooled HR estimate was not different with 0.66 (95% CI: 0.48−0.91; $P = .0179$, Fig. 78.3). Therefore, a common sex category effect could be assumed across centers. Patients with a CRT-D received fewer first appropriate shocks than those without; adding an interaction term of sex category and CRT-D did not change any results. For inappropriate shocks, data from only 3 centers and 1504 patients were available. The incidence of inappropriate shocks was very low; the estimated cumulative incidence curves and their 95% CI did not suggest a sex difference regarding the number of first inappropriate ICD shocks. The HR for female sex adjusted for age, ischemic cardiomyopathy, LVEF$\leq$25%, and CRT-D was 0.79 (95% CI: 0.43−1.42; $P = .47$).

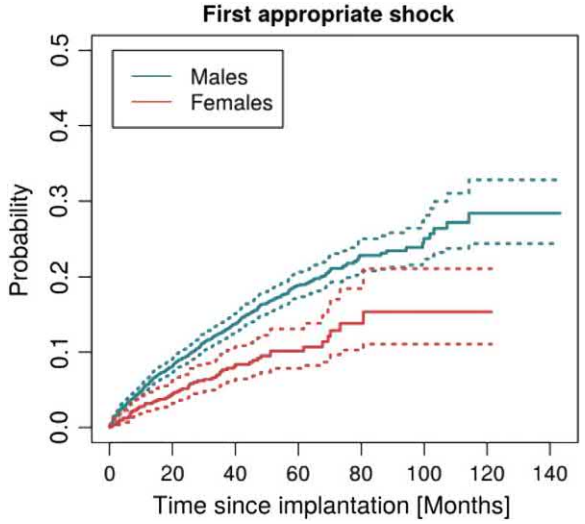

FIGURE 78.2 Cumulative Kaplan−Meier event probability of first appropriate ICD shock in the EU-CERT-ICD combined registry: male (*blue line*) and female (*red line*) patients. 95% confidence intervals are shown in the figure. *EU-CERT-ICD*, Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators in Europe; *ICD*, implantable cardioverter defibrillator. *From Sticherling C, Arendacka B, Svendsen JH, Wijers S, Friede T, Stockinger J, et al. Sex differences in outcomes of primary prevention implantable cardioverter-defibrillator therapy: combined registry data from eleven European countries. Europace. 2018;20(6):963−970 with permission.*

Other multicenter ICD registries

In the French primary prophylactic ICD registry (DAI-PP) [34], only 15% of ICD recipients were female. These authors also confirmed lower rates of appropriate ICD therapies (HR: 0.59; 95% CI: 0.45−0.76; $P < .001$) and a similar overall mortality for women as primary prophylactic ICD patients (HR: 0.87; 95% CI: 0.66−1.15; $P = .324$). Weeke et al. [35] published the results of 1609 primary prophylactic ICD patients from the Danish National ICD registry, enrolled between 2007 and 2011. All patients had ischemic cardiomyopathy; 16% were women. Mortality was low with 12.1% over a mean follow-up of 1.9 ± 1.3 years. Inappropriate shock occurred in 2.6%; appropriate shock occurred in 7.8%. While age and LVEF <25% were significant independent predictors of mortality, the only significant predictor of appropriate shock on multivariate analysis was male sex (HR: 3.99; CI: 1.75−9.12; no *P*-value given). This translates into a 76% lower rate of first appropriate shock in women.

The Israeli ICD registry was reported by Amit et al. [36] and, as one of very few publications on sex differences of ICD outcomes, could not confirm a reduced number of ICD therapies in women after adjustments. This may be due to the fact that only a combined number of appropriate shocks plus appropriate antitachycardia pacing interventions was reported. This registry enrolled 3544 patients between 2010 and 2013, thereof 615 women (17%). Women had the same age and rate of secondary prevention indications but had significantly more heart failure symptoms, wider QRS, and much higher rate of nonischemic cardiomyopathy. Women were more likely to obtain CRT-Ds. Follow-up was available for only 1518 patients and only a mean duration of 12 months. From these data, no significant differences were found for appropriate device therapies or death.

Further multicenter ICD registries do exist, such as the US National Cardiovascular Data Registry (NCDR) ICD [37]. The NCDR was mandated by the Centers for Medicare and Medicaid Services (CMS); however, only baseline data but no follow-up data and ICD therapies were collected. Total mortality is usually available linkable from other registries. In a similar fashion, ICD recipients and/or candidates were retrieved from the Get With The GuidelinesμHeart Failure (GWTG-HF) registry [38]. Zeitler et al. [39] matched 490 elderly women with an ICD with 490 women without ICD using propensity scores (out of a total of 3171 women qualifying). Information from the NCDR, the CMS, and the GWTG-HF were used; enrollments to the

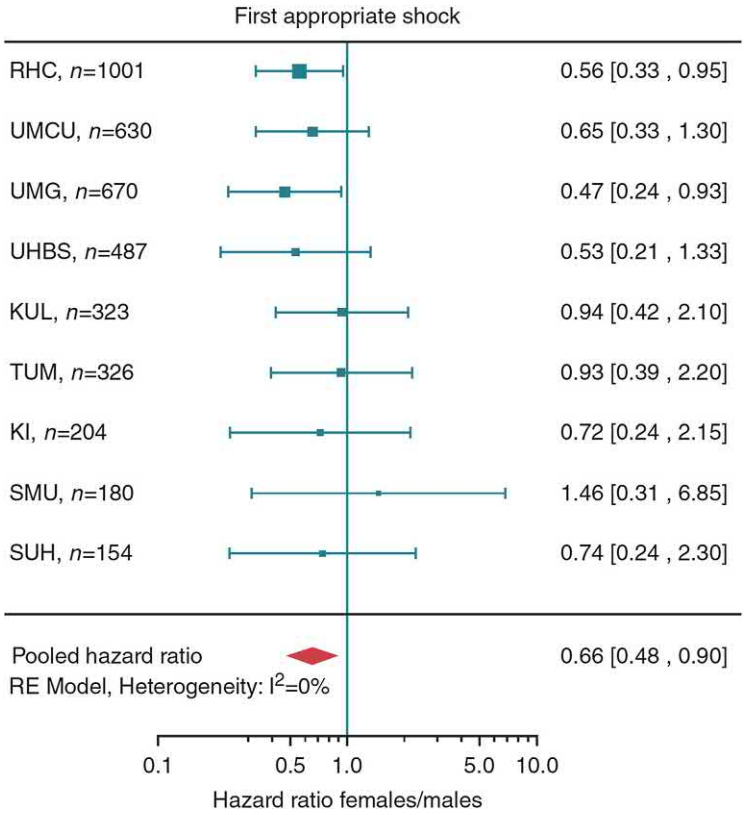

FIGURE 78.3 Forest plot of estimated center-specific hazard ratios for sex category regarding the first appropriate shock together with their 95% confidence intervals and the pooled hazard ratio with a modified Knapp–Hartung 95% confidence intervals. (Note that only centers with at least 10 female patients and at least one observed first appropriate shock both among males and females were included in this analysis.) *From the EU-CERT-ICD combined registry, from Sticherling C, Arendacka B, Svendsen JH, Wijers S, Friede T, Stockinger J, et al. Sex differences in outcomes of primary prevention implantable cardioverter-defibrillator therapy: combined registry data from eleven European countries. Europace. 2018;20(6):963–970 with permission.*

registries were from 2006 to 2007. In the matched cohorts, the survival of women with an ICD was significantly longer than that of women without an ICD (adjusted HR: 0.79; 95% CI: 0.66–0.95; $P = .013$). Similarly, men with an ICD had improved survival compared with men without an ICD (adjusted HR: 0.73; 95% CI: 0.65–0.83; $P < .0001$). There was no interaction between sex and the presence of an ICD with respect to survival ($P = .44$). It has to be reflected that women in this study had an average age of 80 years (75 years in the matched cohort). Data were retrieved retrospectively, and no information about ICD shocks or ICD therapies was available. The longitudinal ICD registry in the United States [40] was developed from the NCDR to add follow-up information and used 14 sites to enroll 2621 ICD patients implanted between 2006 and 2009. During follow-up until 2012, ICD shocks and ICD therapies were recorded. It was noted that the patients enrolled in this registry were older than patients in the randomized ICD studies; however, they were not dissimilar to the overall NCDR ICD registry patients. Among 2235 analyzable patients from the longitudinal registry, a 2.2 ± 0.9 year follow-up was available [41], mean age was 69 ± 11 years, 25% of the patients were women, and 77% were white. There was a high burden of comorbidities, which was associated with a higher burden of device therapies, not necessarily appropriate therapies. Appropriate shock occurred in 18% of patients; inappropriate therapies occurred in 10% of patients. No data on sex-related differences have been reported yet.

Sex differences of ICD outcomes in metaanalyses

With sex-related differences observed in the ICD landmark trials and an overall small number of women enrolled, it was useful to assemble metaanalyses from the available data. Ghanbari et al. [42] published the first metaanalysis of sex-related differences using data from five major ICD studies (MUSTT, MADIT-II, DEFINITE, SCD-HeFT, DINAMIT). A total of 934 women were analyzed; about half their number were implanted an ICD. As a main result, the authors reported that ICD therapy for primary

prevention in women did not show a benefit versus control patients without ICD concerning all-cause mortality (HR: 1.01; CI: 0.76−1.33; $P = .95$). In obvious contrast, the ICD had a 22% mortality benefit among the 3810 men enrolled in the aforementioned five studies (HR: 0.78; CI: 0.70−0.87; $P < .001$). A second metaanalysis of sex-related ICD benefit was published by Santangeli et al. [43] and was somewhat contradictory to the findings of Ghanbari et al. [42]. Very similar ICD studies were included, the DINAMIT trial was omitted, whereas the data from COMPANION were added. Now, pooling four major studies with 1145 women randomized, the authors showed that women had no significant difference in overall mortality (HR: 0.96; CI: 0.67−1.39; $P = .84$). The finding that women experienced significantly less appropriate ICD interventions (HR: 0.63; CI: 0.49−0.82; $P < .001$) was in line with Ghanbari et al. [42] and other studies. Importantly, the ICD benefit on mortality was significantly higher in men (HR: 0.67; CI: 0.58−0.78; $P < .001$) but did not reach statistical significance in women although the HR was also lower than in the analysis by Ghanbari et al. (HR: 0.78; CI: 0.57−1.05; $P = .10$). The main difference between the two metaanalyses was the inclusion of a prophylactic CRT-D trial (COMPANION) by Santangeli et al. [43]. In CRT-D trials, the response of women to resynchronization has been revealed to be better than that of men [44,45], so it is probably necessary to view cardiac resynchronization data separately when judging sex-related differences in outcomes. Taken together, the first two metaanalyses supported that sex has an impact on effectiveness of primary prevention ICD therapy, especially because women seem to have a lower incidence of appropriate shock from the device. This may or may not translate into an absent ICD survival benefit depending on the population of women actually considered.

In parallel to the EU-CERT-ICD metaanalysis described in the following, Barra et al. [46] compiled a metaanalysis adding the recently published DANISH-ICD study [47] to the studies already involved in the previous metaanalyses by Ghanbari et al. [42] or Santangeli et al. [43]. Adding the data from DANISH study to the MUSTT, MADIT-II, DEFINITE, COMPANION, and SCD-HeFT resulted in 5356 men and 1578 women for analysis. In men, the pooled data showed a clear mortality benefit compared with optimal medical treatment alone (HR: 0.75; 95% CI: 0.67−0.84; $P < .001$). In contrast, ICD treatment was not associated with improved survival in female patients in the pooled analysis (HR: 0.93; 95% CI: 0.68−1.27; $P = .63$). When removing the data from the COMPANION trial (CRT-D), the pooled HR was 1.01 (95% CI: 0.73−1.39; $P = .96$). When using data from the long-term follow-up of MADIT-II [48], the pooled HR was 0.95 (95% CI: 0.73−1.22; $P = .67$). The analyses of Barra et al. [46] so far had the largest number of women in one of the available metaanalyses.

EU-CERT-ICD metaanalysis

As most but not all of the prior studies had shown that women receiving a primary prophylactic ICD exhibited a lower risk of death and appropriate shocks than men, a metaanalysis of the available studies in the literature was also conducted within the EU-CERT-ICD project by Conen et al. [20]. The influence of sex category on the risk of appropriate shock, all-cause mortality, and inappropriate shock in contemporary studies of patients receiving a primary prophylactic ICD was targeted. Other than previous metaanalyses limited to randomized studies, the year 2010 (with respect to the publication) was chosen as a starting date to find studies that had enrolled predominantly primary prophylactic ICD patients after the publication of major landmark trials and corresponding guidelines in the field. A predefined list of baseline characteristics, including sex category, age, ischemic cardiomyopathy, NYHA functional class, LVEF, creatinine concentration and/or glomerular filtration rate, QRS duration, diabetes mellitus, type of device, and primary versus secondary prevention, was extracted. Of 680 abstracts identified in the search strategy, 20 studies including 46,657 patients had sex-specific information on at least one of the chosen endpoints [9,12,14,15,34,35] [49−58]. Except four studies, all publications presented primary prevention ICD patients only. The mean age in the various studies ranged between 58 and 69 years. The percentage of women enrolled ranged from 10% to 30%. Across six studies, women had a 38% lower risk of first appropriate shock as compared with men (pooled multivariable adjusted HR: 0.62; 95% CI: 0.44−0.88) (Fig. 78.4). Across 14 studies reporting multivariable adjusted sex-specific HR estimates for all-cause mortality, women had a lower risk of death than men (pooled HR: 0.75; 95% CI: 0.66−0.86) (Fig. 78.5). No difference was found for first inappropriate shocks (three studies, pooled HR: 0.99; 95% CI: 0.56−1.73). In conclusion, in this large contemporary metaanalysis, women had a significantly lower risk of appropriate shocks and death than men, but a similar risk of inappropriate shocks.

Sex differences in adverse events following implantable cardioverter defibrillator implantation

Several registry studies have revealed sex-related disparities with regard to adverse events after ICD implantation. Peterson et al. reported on the effect of sex category on the number of complications associated with

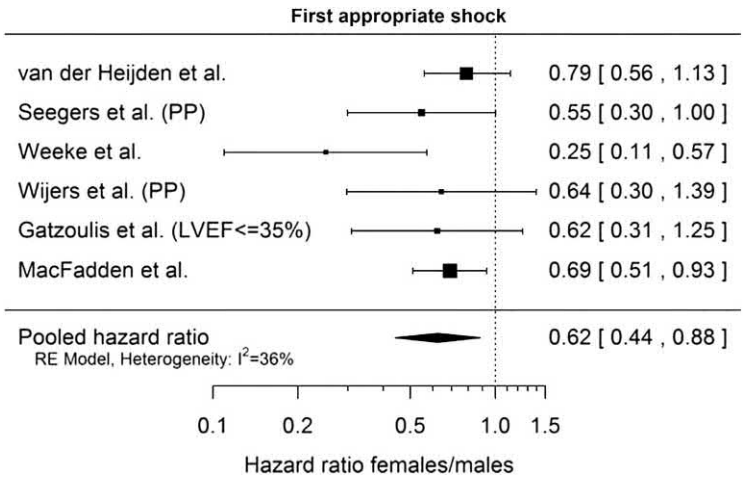

FIGURE 78.4 Extracted hazard ratios for female sex regarding risk of first appropriate shock with 95% confidence intervals as reported in the respective publications. "PP" indicates that the results were reanalyzed for primary prevention patients only. The pooled estimate is reported with a Knapp–Hartung adjusted 95% confidence interval. The dotted vertical line denotes a hazard ratio of 1, which corresponds to no difference in the risk between males and females. *From Conen D, Arendacka B, Rover C, Bergau L, Munoz P, Wijers S, et al. Gender differences in appropriate shocks and mortality among patients with primary prophylactic implantable cardioverter-defibrillators: systematic review and meta-analysis. PLoS One. 2016;11(9):e0162756. with permission.*

ICD implantations [17]. From the NCDR ICD registry, data of 161,470 patients were reviewed, and 27% of these were female. There was a higher rate of complications in women as compared with men (4.4% vs. 3.3%, $P < .001$). A higher complication rate in female ICD recipients was also confirmed by Amit et al. from the Israeli ICD registry [36] and in the study by MacFadden et al. from the Ontario ICD registry [9]. In the latter report, complications after ICD implantation were more frequent in women as compared with men. This was found after 45 days for any major complications (men: 3.3%; women: 5.4%; odds ratio: 1.78; CI: 1.24–2.58; $P = .002$) and any minor complications (men: 3.8%; women: 5.8%; odds ratio: 1.55; CI: 1.09–2.20; $P = .006$). It was also true for any major complications within 1 year (odds ratio: 1.91; CI: 1.48–2.47; $P < .001$) and any minor complications within 1 year (odds ratio: 1.56; CI: 1.17–2.08; $P = .002$). The increased rate of complications in women needs to be weighed against the presumed benefits of ICD therapy.

Implantable cardioverter defibrillator implantation rates in women

Female underrepresentation has been a consistent problem of all primary prevention ICD trials [4–6,47].

One main result of the ICD registry work presented was the confirmation that the primary prevention ICD implantation rate is consistently low in women across many countries (19% with a range between 8% and 28% among centers in Ref. [18] and similar in other reports). This was shown in Canada not to be due to underrecruitment [9]. In several reports, women demonstrate a lower overall mortality, which is not entirely understood. Overall, they appear to be healthier viewed from the cardiovascular perspective; for instance, they usually exhibit a lower proportion of ischemic cardiomyopathy and vice versa a higher proportion in nonischemic cardiomyopathy. An additional factor may be that women, in general, have a longer life expectancy than men. After adjustment of these differences in patient characteristics by multivariate statistics, there is still a lower rate of malignant arrhythmias and appropriate shocks.

Summary and discussion of registries and metaanalyses

Multiple ICD registries including three very large registries (Ontario ICD registry [9], EU-CERT-ICD combined registry [18], DAI-PP French registry [34]) confirmed the significantly lower appropriate shock rate in >20,000 women. A lower number of malignant arrhythmias could, however, translate to a lower ICD survival benefit. A lower (or absent) and nonsignificant survival benefit for women (in contrast to the male patients who did benefit significantly) was reported by three metaanalyses between 2009 and 2017 [42,43,46]. A fourth metaanalysis again confirmed the lower appropriate shock rate in women in >46,000 patients [20]. Thus, the available evidence suggests that the risk–benefit ratio might be less favorable in women and the number needed to save one life higher.

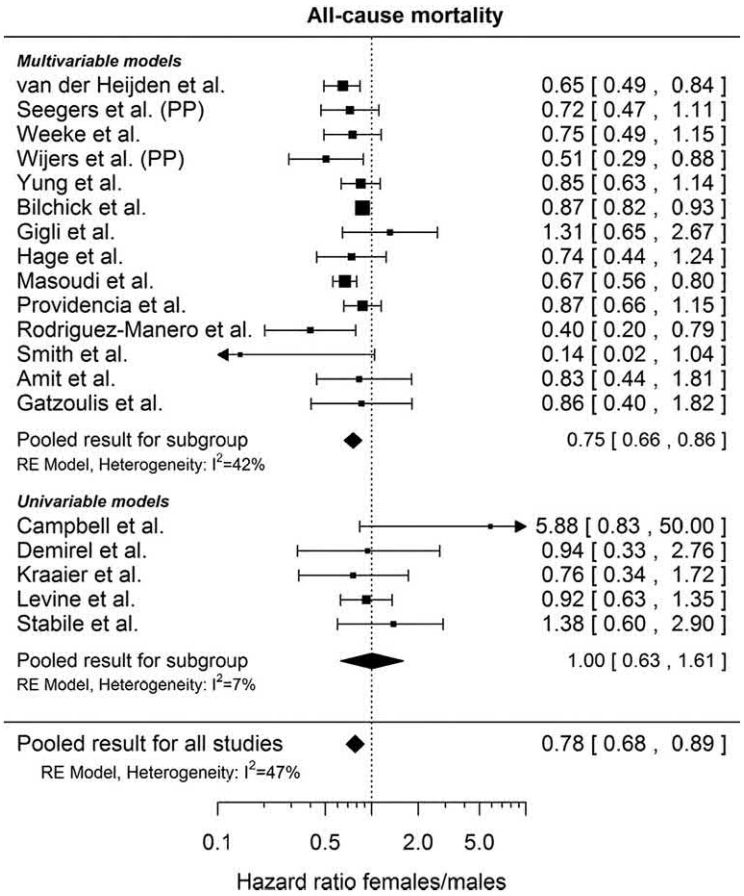

FIGURE 78.5 Extracted hazard ratios for female sex regarding risk of all-cause mortality with 95% confidence intervals as reported in the respective publications. "PP" indicates that the results were reanalyzed for primary prevention patients only. The pooled estimate is reported with a Knapp−Hartung adjusted 95% confidence interval. The *dotted vertical line* denotes a hazard ratio of 1, which corresponds to no difference in the risk between males and females. *From Conen D, Arendacka B, Rover C, Bergau L, Munoz P, Wijers S, et al. Gender differences in appropriate shocks and mortality among patients with primary prophylactic implantable cardioverter-defibrillators: systematic review and meta-analysis. PLoS One. 2016;11(9):e0162756. with permission.*

While primary prophylactic ICD therapy should not be withheld in women, improved risk stratification is needed to allocate primary prophylactic ICD treatment, and sex category may be one of many possible risk factors, similar to age, chronic kidney disease, diabetes, atrial fibrillation, or chronic obstructive pulmonary disease [11,50,59]. Analyses from the prospective EU-CERT-ICD nonrandomized controlled study will also analyze sex difference in ICD benefit and are awaited in 2019 [19]. Thereafter, the evidence should be weighed once more for possible consequences in primary prophylactic patient selection for ICD treatment. This also included a potentially higher benefit from CRT treatment. Probably, the decision to implant prophylactic ICDs should be made more individualized, and the data and results of the EU-CERT-ICD retrospective and prospective studies can provide guidance. The lower rate of women currently indicated for ICD treatment does not reflect underrecruitment. New randomized ICD studies should become feasible.

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Chapter 79

Clinical experience with the use of CRT in women

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Introduction

Several randomized clinical trials have shown a clinical benefit, including a reduced morbidity and mortality, with the use of cardiac resynchronization therapy (CRT) in patients with left ventricular dysfunction, mild to advanced heart failure (HF), and wide QRS duration [1−3]. Sex-specific CRT outcomes reported in the past have been scarce and primarily limited by the small number of women in CRT trials due to their underrepresentation in clinical studies [4].

Nevertheless, sex-related differences have been observed in heart failure etiology and pathophysiology. Women are diagnosed with cardiomyopathy at an older age, and they typically present with more comorbidities such as hypertension, obesity, and diabetes, but they less often have ischemic cardiomyopathy [5−7]. Women also more often have diastolic dysfunction, and they tend to have a higher left ventricular ejection fraction than men [8,9]. Despite having a higher ejection fraction at disease onset, women often present with worse New York Heart Association (NHYA) class [10]. Despite these facts however, women are treated less aggressively for heart failure, and they receive less ICD or CRT devices in accordance with guideline-recommended treatments [11,12]. According to the American Heart Association, women comprise only approximately 30% of CRT device implantations [11]. A recent FDA guidance document called for action on increasing the inclusion of women and minorities in medical device trials and reporting sex-specific outcomes (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-and-reporting-age-race-and-ethnicity-specific-data-medical-device-clinical-studies).

In this chapter, we will review currently available data on clinical experience with the use of CRT in women, including information on outcomes from clinical trials, large registries, and metaanalyses, and focus on complication rates, outcomes of echocardiographic reverse remodeling, and clinical outcomes of heart failure or death during short-term and long-term follow-up. We will also discuss pathophysiological differences between men and women and its relation to CRT outcomes.

Randomized controlled trials

Among all randomized controlled trials (RCTs) on CRT outcomes, LVEF, QRS duration, and age were similar between men and women. However, more than half of the studies had less than 25% of women enrolled, thereby significantly limiting analysis on sex-specific outcomes.

In one of the early CRT studies, the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study [13], that included a relatively high percentage of women in comparison with other RCT (32% were women), women receiving CRT experienced longer times to first HF-related hospitalization or death (HR = 0.157), whereas there were no improvements in either HF hospitalization or death, or HF alone [14].

However, in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, which included also a high percentage of women (32%), there was a significant reduction in death and hospitalization in the trial as a whole with no difference between men and women [15]. Similar findings were shown in the Cardiac Resynchronization−Heart Failure (CARE-HF) trial as well, including patients with more advanced HF symptoms of NYHA class III or IV [16]. Both COMPANION and CARE-HF, however, enrolled a relatively small percentage of women in the study.

The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT trial) was one of the first studies to describe significant

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sex differences in CRT outcomes and encourage and remind physicians to enroll a high enough proportion of women in the study. MADIT-CRT enrolled 1820 patients, of whom 453 (25%) were women (Table 79.1). Eligible patients had NYHA class I and II symptoms, LVEF 30%, and QRS duration ≥130 ms. Patients were randomized to CRT with defibrillator (CRT-D) or ICD alone, with the primary outcome measure being HF events or death. Women in MADIT-CRT were more likely to have a non-ischemic etiology of cardiomyopathy and left bundle branch block (LBBB) morphology. Women in MADIT-CRT were found to have significantly greater left ventricular reverse remodeling, characterized by the significant improvement in LVEF, left ventricular end-systolic volume, and left ventricular end-diastolic volume, as compared with men [17]. The primary endpoint of heart failure or death was met in 16% of women with CRT-D versus in 30% of men at 4-year follow-up compared with 41% event rate in women with an ICD versus 36% event rate in men with an ICD (log rank P for the total duration of time $<.001$). The relative risk reduction in HF or death events in women with CRT-D versus an ICD-only was 69% ($P < .001$) compared with a 28% risk reduction in men with CRT-D versus ICD-only (interaction P-value$<.01$). Interestingly, survival benefit was observed for women with CRT-D versus ICD-only with a 72% relative risk reduction as compared with no survival benefit in men (HR = 1.05) [17]. Another substudy from MADIT-CRT by Tompkins et al. additionally corroborated effects of CRT on ventricular tachyarrhythmia events showing that both sex and disease etiology play an important role. In this study, the probability of ventricular tachycardia (VT), ventricular fibrillation (VF), or death was lower in women than in men (HR = 0.62, $P < .001$), and it was the lowest in women with ischemic heart disease (HR = 0.51, $P = .003$). In addition, women with appropriate shock therapy were at a more than fivefold increase at death as compared with men at a 63% increased risk of death (interaction $P = .034$), suggesting that once women experience an ICD therapy, they are at a higher risk of adverse outcomes. We also have to acknowledge that there is a greater risk of device related complications in women with implantation of a CRT device. Jamerson et al. showed that women in MADIT-CRT were twice as likely to experience a major procedure-related adverse event as compared with men (6.3% vs. 2.7%, $P < .001$) [18].

In the Resynchronization for Ambulatory Heart Failure (RAFT) trial, however, there was a significant and comparable mortality benefit in both men and women [19].

In the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study, there were 114 women (19%) enrolled, who showed a greater degree of left ventricular revere remodeling than men, but similar reduction in HF or death with CRT ON [20]. This study, however, had one of the lowest proportions of enrolled women, and it likely has a limited power to detect sex differences in CRT outcomes.

Do women really benefit more from cardiac resynchronization therapy more than men? And why?

Several important differences in baseline clinical characteristics exist between men and women, which may contribute to better outcomes in women. Current analysis of

TABLE 79.1 Summary of CRT outcomes in women versus in men in controlled clinical trials.

Clinical trial	Patients (n)	Primary end points	Number of women (%)	LVEF (%)	QRS (ms)	Outcomes in women versus men
MIRACLE	453	6MWT, NYHA class, QoL	145 (32%)	22%	166	Women had better outcomes than men
COMPANION	1520	All-cause mortality or hospitalization	486 (32%)	21%	159	Similar efficacy in men and women
CARE-HF	814	All-cause mortality	211 (26%)	25%	160	Similar efficacy in men and women
REVERSE	610	HF clinical composite score	114 (19%)	27%	153	Similar efficacy in men and women
MADIT-CRT	1820	HF or death	453 (25%)	24%	162	Women had significantly better outcomes than men
RAFT	1798	All-cause mortality or HF hospitalization	308 (17%)	23%	158	Women had slightly better outcomes than men

CARE-HF, Cardiac Resynchronization—Heart Failure; *COMPANION,* Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; *CRT,* cardiac resynchronization therapy; *HF,* heart failure; *LVEF,* left ventricular ejection fraction; *MADIT-CRT,* Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy; *MIRACLE,* Multicenter InSync Randomized Clinical Evaluation; *NYHA,* New York Heart Association; *QRS,* QRS duration; *RAFT,* Resynchronization for Ambulatory Heart Failure; *REVERSE,* Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction.

clinical trials clearly demonstrates the great benefit of CRT among patients with LBBB, whereas multiple studies suggested that CRT is less effective or can be even harmful in patients without LBBB [21–23]. Women more frequently present with nonischemic cardiomyopathy, and more often present with LBBB, and these factors all predict superresponse to CRT [24]. In a large analysis of the NCDR ICD Registry patients, Zusterzeel et al. included 31,892 patients who underwent CRT-D, just like in MADIT-CRT, women had a significantly higher proportion of LBBB at baseline and better CRT response than men [25,26]. Even though retrospective studies adjusted for differences in clinical characteristics such as LBBB, or disease etiology by sex and identified sex as an independent risk factor, further analyses are warranted to fully elucidate whether sex differences have intrinsic components or just serve as a specific, and highly sensitive, marker for specific disease characteristics.

Interestingly, since women have smaller hearts and a physiologic shorter QRS duration at baseline compared with men, they may also have a more advanced electrical substrate and more frequent "true LBBB" even at a shorter QRS duration than men [27]. Individual patient data metaanalysis found that women with LBBB benefited from CRT-D compared with ICD with QRS $\geq$ 130 ms, whereas men with LBBB and the same HF stage benefited from CRT-D only at a QRS $\geq$ 150 ms. However, the diagnosis of a true LBBB remains challenging. Electrophysiology studies and preclinical data have shown that only 66% of patients diagnosed with LBBB by surface ECG have endocardial activation disorder consistent with true LBBB [28,29].

Sex-specific outcomes by QRS duration were further studied by Varma et al., showing that although the QRS duration was shorter in women, QRS duration divided by BSA or divided by LV mass was 10% and 54% greater. This suggests that women might have a relatively greater electrical dyssynchrony when adjusted for body size or LV size, and this could likely explain inherent sex differences in CRT response [30]. They also showed that the relationship between QRS duration and CRT response by sex is unique, and women showed a high response rate for relatively narrow QRS durations of 135–150 ms but a decline for QRS > 170 ms. Men, on the other hand, demonstrated lower probability of response for narrower QRS durations and a plateau for wider QRS (Fig. 79.1A). Similar findings were revealed from the MADIT-CRT long-term follow-up study when assessing sex differences; women were shown to have a significant reduction in long-term HF or death event with QRS < 150 ms (HR = 0.31), whereas men with QRS < 150 ms derived no significant, long-term benefit from CRT-D versus ICD (HR = 0.80). These findings altogether suggest a significant modifying effect of QRS duration by sex, and indeed, one could ask whether there is a need for sex-specific guidelines for implantation of CRT [32]. While current guidelines do not provide sex-specific recommendations, physicians need to be keenly aware and take into consideration sex-specific risk factors and characteristics, when assessing the need and likelihood of response to CRT.

Other factors that may have contributed to a greater CRT effect in women compared with men are the etiology of cardiomyopathy, scar burden, and the presence of concomitant atrial fibrillation. In all RCTs, men have significantly more ischemic cardiomyopathy at origin than women, and in some of these studies, the rate was twice as high as in women. Multiple prior studies have shown that ischemic cardiomyopathy is associated with worse prognosis, less remodeling, and less improvement in clinical

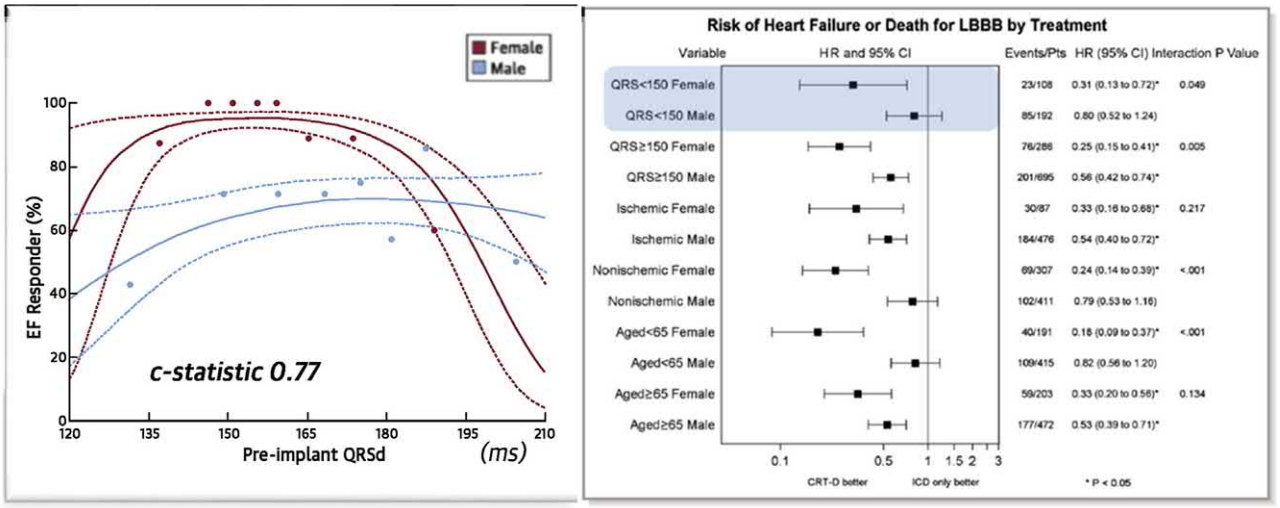

FIGURE 79.1 (A and B) Probability of CRT response according to QRS duration and sex [30]; long-term CRT outcomes by QRS duration and sex [31]. *CRT*, cardiac resynchronization therapy. Reproduced from *Varma N, Lappe J, He J, Niebauer M, Manne M, Tchou P. Sex-specific response to cardiac resynchronization therapy: effect of left ventricular size and QRS duration in left bundle branch block. JACC Clin Electrophysiol. 2017;3(8):844–53 and Biton et al. JAHA, 2015, needs permission.*

outcomes of HF or death as compared with patients with nonischemic cardiomyopathy, even after implantation of CRT and the use of guidelines-directed medications [33,34]. Importantly, some recent studies also suggested that women have a lower proportion of scar burden and less fibrosis, which could explain why the benefit is greater in women as compared with men. In an elegant study by Loring et al. [35], 235 patients underwent cardiac MRI before primary prevention of ICD implantation. Scar burden was evaluated by sex and by disease etiology. Overall, women had smaller myocardial scar sizes than men (0.5% vs. 13%, $P < .001$). Interestingly, scar burden was similar by sex in nonischemic cardiomyopathy. In nonischemic cardiomyopathy patients, women had less scar zones, smaller core zones, and gray zones. Scarring in women was less significant than in men especially in the inferolateral region (segments 4, 5, 10, 11) that is most frequently targeted for the delivery of CRT (Fig. 79.2). Studies showed that patients implanted with LV leads in scar region had a suboptimal response to CRT, and this is a likely an important contributor to the lower rate of response to CRT in men [36–39].

Another relevant factor is left ventricular dyssynchrony that has been shown to be an important determinant of CRT response [40–42]. While there are relatively limited studies conducted on sex differences in left ventricular dyssynchrony in HF patients, one of our substudies from MADIT-CRT suggested that women have a greater degree of left ventricular dyssynchrony at any given QRS duration as compared with men (Solomon et al., unpublished). This finding is in alignment with other observations on mechanical dyssynchrony measured by QRS duration and sex-specific CRT outcomes. These studies altogether point to an advanced electromechanical substrate in women without significant scar tissue formation that predisposes women to a high risk of HF events while they are remaining at a lower risk of ventricular arrhythmia events. Such an electromechanical substrate is optimal for implantation of CRT and explains why women have superior response to CRT as compared with men.

There is another consideration that needs to be addressed. Since women often present with nonischemic cardiomyopathy, LBBB, and less scar and exhibit superior response to CRT with significant increase in left ventricular ejection fraction and reduction in left ventricular volumes, some might argue that women would do well with a CRT-P (pacemaker) device only. This is supported by an intriguing analysis by Barra et al. [43] who showed a CRT-D was beneficial in male patients using inverse probability weighing (HR = 0.78, $P = .12$), but not in women (HR = 0.87, $P = .43$). The excess mortality in the CRT-P group in this study was related to sudden cardiac death in 7.4% of the cases in men but only in 2.2% of the cases in women. Such argument is further supported by an earlier analysis showing that CRT-D was associated with an incremental survival benefit in patients with nonischemic cardiomyopathy (HR = 0.70, $P = .03$), but not in nonischemic cardiomyopathy (HR = 0.98, $P = .894$). In this study, women were twice as likely to be implanted with CRT-P as compared with CRT-D (29% vs. 16%). Outcomes in a large US remote monitoring database showed that women had superior outcomes to men when implanted with a CRT-D, but also when implanted with a CRT-P device. This suggests that even CRT-P therapy is associated with sex differences in outcomes and could potentially be utilized in future cohorts. Implantation of CRT-P devices is linked to less complications, a concern that' is particularly relevant for women.

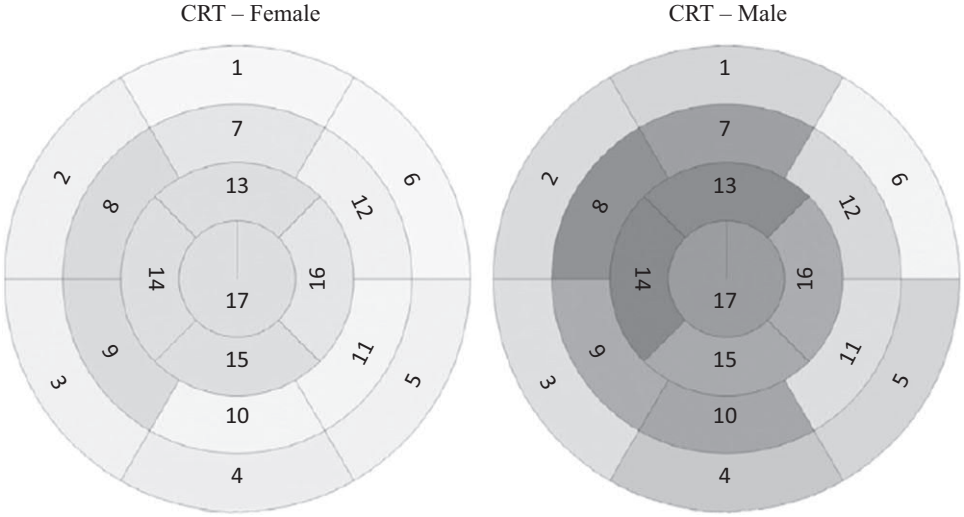

FIGURE 79.2 Circumferential polar plot of scar transmurality distribution by sex for CRT patients. *CRT*, cardiac resynchronization therapy. *Loring Z, Strauss DG, Gerstenblith G, Tomaselli GF, Weiss RG, Wu KC. Cardiac MRI scar patterns differ by sex in an implantable cardioverter-defibrillator and cardiac resynchronization therapy cohort. Heart Rhythm. 2013;10(5):659–65.*

Sex-specific cardiac resynchronization therapy use in selected registries and metaanalyses

A few most relevant studies assessing sex-specific CRT outcomes in nonrandomized registries and metaanalyses are summarized in Table 79.2. Importantly, all of these studies are unanimously pointing to better CRT outcomes, and an improved survival in women than in men, including heterogeneous study populations with a low ejection fraction and a wide QRS. Two metaanalyses by Cheng et al. [44] and Loring et al. [45] further substantiated these findings. Cheng et al. showed a 33% lower risk of death from any cause in women as compared with men, as well as a 20% lower risk of HF or death, a 41% lower risk of cardiac death, and a 41% lower risk of ventricular arrhythmias or sudden cardiac death. Loring et al. [45] analyzed ~145,000 patients using Medicare records between 2002 and 2008 and identified a significant interaction between sexes ($P < .001$) with a 26% risk reduction in death in women with LBBB versus 15% in men with LBBB, after multivariable adjustments.

Altogether, the evidence on sex-specific differences in CRT outcomes is significant, and physicians need to take into consideration sex-specific characteristics when assessing the likelihood of response to CRT. This is already highlighted in guideline documents and useful for practicing clinicians (Fig. 79.3).

TABLE 79.2 Summary of sex-specific outcomes with CRT in nonrandomized studies, registries, and metaanalysis.

Title	Author, y	Study design	Patients (n)	Primary end points	Number of women (percentage)	LVEF (%)	QRS (ms)	Outcomes in women versus men
Sex-specific difference in outcome after cardiac resynchronization therapy	Beela et al. [45]	Retrospective analysis of data from multicenter registry	1,058	All-cause mortality	254 (24%)	26 ± 6	168 ± 23	Better outcomes in women in univariate analysis
Female gender is associated with a better outcome after cardiac resynchronization therapy	Leyva et al. [46]	Observational study	550	All-cause mortality	122 (22%)	23.5 ± 11.7	152.1 ± 26.2	Better outcomes in women than in men
Women have better long-term prognosis than men after cardiac resynchronization therapy	Zabarovskaja et al. [47]	Retrospective analysis of data from multicenter registry	619	All-cause mortality	118 (19%)	24 ± 8.3	160 ± 27	Better outcomes in women than in men
More favorable response to cardiac resynchronization therapy in women than in men	Cheng et al. [43]	Metaanalysis	33,434	All-cause mortality	8,058 (24%)	18%–28.4%	146–180	Better outcomes in women than in men
Left bundle branch block predicts better survival in women than men receiving cardiac resynchronization therapy	Loring et al. [44]	Metaanalysis	144,642	All-cause mortality	37,167 (26%)	NA	NA	Better outcomes in women than in men

LVEF, left ventricular ejection fraction; *NA*, not available.

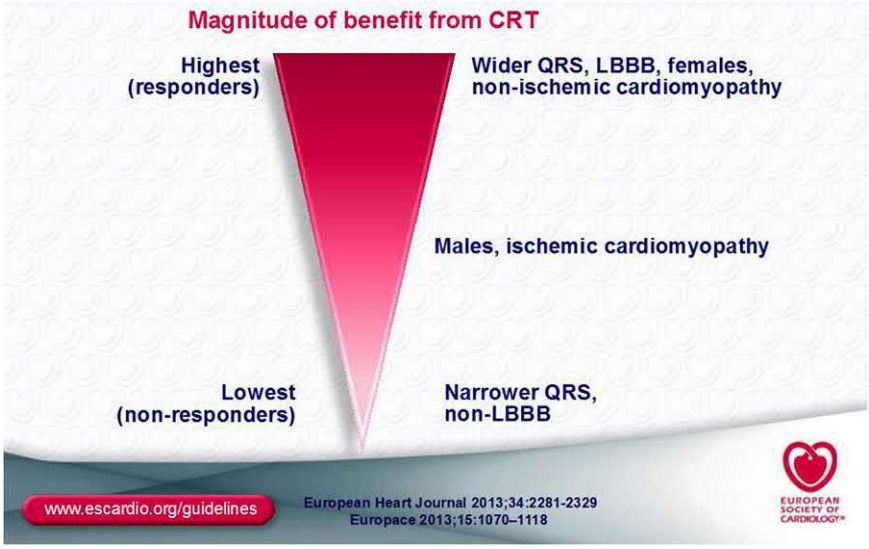

FIGURE 79.3 Magnitude of benefit from CRT. *CRT*, cardiac resynchronization therapy.

Further increase of women enrolled in CRT clinical trials will enable us to better understand sex-specific differences in outcomes. Identification of women candidates for CRT is relevant not only in clinical trials but also in clinical practices to ensure that access to treatment modalities such as CRT is equal for both sexes. Further pathophysiology studies will enable us to better understand the causal relationship between sex and CRT outcomes. In addition, in the future, better information tools for physicians and patients on sex-specific outcomes and risks with CRT should be available to aid decisions on CRT implantation in HF patients.

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Chapter 80

CRT and sex-specific registries and metaanalyses

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Introduction

The benefit of cardiac resynchronization therapy (CRT) is well documented. Cardiac resynchronization therapy reduce mortality and morbidity in patients with heart failure (HF) secondary to reduction in left ventricular ejection fraction—LV systolic dysfunction, and evidence of dyssynchronous electrical activation and therefore delayed LV activation, secondary to LBBB [1−6] especially if prolonged QRS duration and specifically greater benefit if QRS is wider than 150 ms [6−8].

In the following chapter, we describe and summarize data of the efficacy and effectiveness of CRT in women as compared with men based on data from large randomized clinical trials, observational data from registries, single- and multicenter reports, and metaanalyses.

Data from clinical trials

Data from randomized controlled trials on the effect of CRT in women are limited. Women represented a minority of patients recruited in the large randomized trials of CRT, ranging from 23% to 32% [1,9].

The MIRACLE study [1] (453 patients, 32% women) and the MIRACLE ICD study [9] (369 patients, 23% women) included HF patients in New York Heart Association (NYHA) functional class (FC) III−IV, ejection fraction (EF) of ≤35%, left ventricle end-diastolic diameter (LVEDD) of ≥55 mm, and a QRS duration (QRSd) of ≥130 ms. Women were less likely to have progressive remodeling at follow-up and more likely to have reverse remodeling as measured by left ventricle end-diastolic volume (LVEDV) as compared with men. This was seen in both ischemic and nonischemic CMP (NICMP) [10]. The COMPANION (2) (1520 patients, 32% women) and CARE-HF [3] (813 patients, 27% women) trials enrolled patients with HF in NYHA class III or IV, an EF ≤ 35%, and a QRSd ≥ 120 ms to randomly receive resynchronization therapy or optimal medical therapy. Both trials showed a similar benefit with CRT in men and women with respect to death and HF [2,3].

The REVERSE trial [11] (610 patients, 22% women) included patients with HF in NYHA FC I or II, with a QRS ≥120 ms and an LV EF ≤ 40%, who received a CRT device and were then randomized to have the device on or off. Patients assigned to CRT-ON experienced a greater reduction in LV end-systolic volume index and other measures of LV remodeling [11]. Time-to-first HF hospitalization was also significantly delayed. Women had a similar clinical benefit as men with respect to worsening HF but a numerically larger decrease in indexed left ventricle end-systolic volume (LVESV) (27.9 vs. 13.4 mL in men).

Finally, in the Resynchronization−Defibrillation for Ambulatory Heart Failure Trial (RAFT) (1798 patients, 19% women) [12] that recruited patients with class II or III HF, an EF ≤ 30%, and QRSd ≥ 120 ms. CRTD was better than implantable cardioverter defibrillator (ICD) for prevention of HF and death [12]. Although no significant interaction between treatment benefit with CRT and sex was seen, the benefit was numerically larger in women as compared with men [12].

MADIT-CRT [13] recruited 1820 patients (25% women) with an EF ≤ 30% and a QRS ≥130 ms and mild HF symptoms (NYHA I−II) to receive either an ICD or CRTD. CRTD significantly reduced the primary composite of HF deaths and nonfatal events, with a signal for greater benefit in women than in men [13]. A separate analysis was performed using data from the original trial comparing women and men in terms of clinical and echocardiographic outcomes [14]. Women were more likely to have NICMP and LBBB than male patients, whereas men were more likely to have ischemic heart disease, prior coronary

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revascularization, and renal dysfunction. Women had a larger benefit from CRTD therapy: They had a significant 69% reduction in death or HF (28% reduction in men) and a 70% reduction in HF alone (35% reduction in men). In addition, they had a significant 72% reduction in all-cause mortality, which was not seen in men [14] (Fig. 80.1). Similar findings were seen in different HF etiologies, with or without LBBB and regardless of QRSd [14].

Furthermore, the better outcomes observed after CRTD in women were also associated with consistently greater echocardiographic evidence of reverse cardiac remodeling in female compared with male subjects with respect to decrease in LVESV and LVEDV and increase in left ventricle ejection fraction (LVEF) [14]. Of note, in this study, women had a higher likelihood of device-related adverse events. An additional analysis from MADIT-CRT [15] limited to patients with LBBB morphology showed that women with CRT had a larger benefit with respect to reduction in the risk of HF or death (41% reduction in men vs. 71% reduction in women) that was also statistically significant [15].

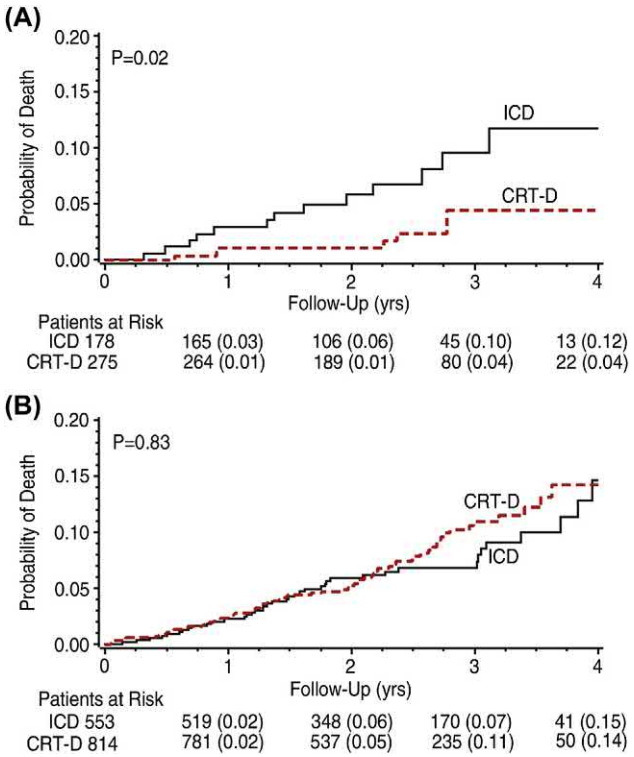

FIGURE 80.1 Kaplan–Meier estimates of the cumulative probability of death in women and men by device therapy. (A) Women had a significantly lower probability of death over time with CRTD (*red line*) than with ICD (*black line*). (B) Men had similar probability of death over time with CRTD therapy (*red line*) or with ICD therapy (*black line*) [14]. *CRTD*, cardiac resynchronization therapy defibrillator; *ICD*, implantable cardioverter defibrillator.

Observational data from single- and multicenter studies comparing cardiac resynchronization therapy in men and women

Single- and multicenter observational studies

Leyva et al. [16] showed that among patients (n = 550, women 22%) treated with CRT, 6-min walking distance increased by 85 ± 117 m in women and by 66 ± 107 m in men. Women exhibited a greater reduction in LVESV (23% vs. 11% $P = .0445$) and a greater increase in LVEF (9.2% vs. 3.5%, $P < .05$). Female sex was associated with lower risk of death (HR: 0.52; 95% CI: 0.34–0.79), as well as HF hospitalization and CV death even after accounting for QRS duration and HF etiology [16].

Wang et al. [17] in a single-center study compared men and women ≥ 75 years old with HF in NYHA III–IV who underwent CRT implantation between 2002 and 2013 (n = 512 patients, 149 women, 29%). In their study, women had less often coronary artery disease and more often LBBB. The average QRS duration (QRSd) was 150 ms in women and 160 ms in men. Mortality risk of women was significantly lower as compared with men (HR: 0.75; 95% CI: 0.58–0.99) although it was of only borderline significance after multivariate adjustment (HR: 0.79; 95% CI: 0.59–1.05).

Varma et al. [18] in a study of 212 patients (105 women, 50%) with NICMP, HF, and complete left bundle branch block (CLBBB) implanted with CRT showed that women had a significantly better improvement of LVEF as compared with men (15% vs. 7%). Furthermore, this favorable response was independent of QRS width in women (83% in women with QRSd < 150 ms and in 86% of women with QRSd of >150 ms), whereas in men, this response was dependent on QRSd (69% responders in men with QRSd > 150 ms and 36% response in men with QRSd < 150 ms). In a subgroup of this study population, Varma et al. [19] showed that women had a greater rate of response to CRT as compared with men in terms of increased EF (90% responders vs. 66% in men in terms of echocardiographic favorable response) and larger decrease in LVEDD and LVESD [19]. The response was highly dependent on QRSd >150 ms in men and less so in women [19]. The threshold of QRSd associated with improvement in women was 135 ms [19]. However, after normalization of QRSd to LV mass, these discrepancies between men and women disappeared, and a uniform response was seen in both sexes [19], demonstrating that the association between response to CRT and QRSd may be more complex and also related to differences in LV mass between men and women.

In a study, conducted at two Italian heart transplantation centers between 1999 and 2010, of 507 patients who received CRT (20% women, a large proportion of patients

with NICMP) [20], women had a trend toward lower risk of death and cardiovascular death as compared with men. However, this difference was only seen in patients with NICMP and not among those with ischemic etiology [20]. Similar to other studies, EF and LVESV improved more in women as compared with men (LVEF 12% vs. 5%, LVESV −56.2 vs. −33.1 mL). Improvement in FC, however, was similar in men and women. Furthermore, the rate of responders to CRT in terms of echocardiographic reverse remodeling was significantly larger in women (76%) as compared with men (51%).

In another large single-center study from the Karolinska Institute (n = 619, women 119; 19%), women with CRT had a lower risk of death as compared with men counterparts even after multivariate adjustment (HR: 0.439; 95% CI: 0.214−0.903) [21]. Women also had a lower rate of hospitalizations and a trend to lower rate of HF-specific hospitalizations. NICMP was more common among women than men in this study as was also described in other studies.

A recent multicenter study of 5307 consecutive patients (women = 1158, 22%, 70% NICMP in women vs. 44% in men) with ICMP or NICMP having CRT implantation (CRTD, n = 4037, CRTP, n = 1270) showed significantly lower rates of all-cause death and cardiovascular death in women [22].

In a large single-center study of 728 consecutive CRT patients (166 women, 23%), women had a higher rate of NICMP (68% vs. 36%) and LBBB (63% vs. 42%) as compared with men at baseline. Women had significantly greater improvement in their NYHA class than in men (-0.79 ± 0.78 vs. -0.56 ± 0.85; $P = .009$) [23]. In this study, men and women with LBBB and QRS>150 ms had significant improvements in NYHA FC, EF, and reverse remodeling. Although female sex was associated with echocardiographic improvement in univariate analysis, it was no longer associated with better outcome after taking into account LBBB and HF etiology [23]. Women had lower mortality rates as compared with men (19% vs. 38%). After multivariate adjustment, female sex was no longer associated with lower risk of death, whereas LBBB and NICMP (both of whom more prevalent in women) were associated with lower risk of death. These findings suggest that the observation of better echocardiographic improvement and lower risk of death are related to at least in part to the higher prevalence of LBBB and NICMP in women as compared with men [23].

Observational data from registries and database—electronic health records studies

In a large electronic health records (EHR) study, from the United Kingdom, of patients implanted with CRT (CRTD and CRTP) between 2009 and 2017 (n = 50,084, 39% NICMP, 25% women, 50% CRTD), women had a lower risk of death as compared with men (HR: 0.75; 95% CI: 0.70−0.80) [24]. This effect of lower mortality in women was consistent in both patients implanted with CRTP or CRTD [24].

In the largest available EHR study of Medicare patients implanted with CRTD (25) (n = 144,642, women; 26%), women had more commonly LBBB (53% vs. 39%) and less often ischemic cardiomyopathy (53% vs. 69%) at baseline. Women had lower mortality rate as compared with men (54% vs. 62%) after 6 years of follow-up (Fig. 80.2A). This was observed in patients with LBBB (49% vs. 59%) as well as in men and women without LBBB (60% vs. 64%). Both female sex and LBBB were associated with lower risk of death at follow-up after multivariate analysis (Fig. 80.2). However, LBBB was associated with significantly lower risk of death in women (HR: 0.74; 95% CI: 0.71−0.77) as compared with men (HR: 0.85; 95% CI: 0.83−0.87), and the interaction between female sex and LBBB and lower risk of death was highly significant. These observations were also seen in terms of HF hospitalizations (Fig. 80.3) [25].

Another study included patients with NYHA class III or IV HF and a QRS duration of 120−220 ms (n = 75,159, of the 20,379 were women) [26] who received a first-time CRTD or ICD implant between January 1, 2006, and March 31, 2010. Women had a higher rate of NICMP (55% vs. 31%) and LBBB (80% vs. 61%) at baseline. Women (n = 20,379) as well as men (n = 42,560) implanted with CRTD had significantly lower mortality rates as compared with patients implanted with ICD (Fig. 80.4). However, this reduction in mortality risk was significantly more pronounced in women (HR = 0.77; 95% CI: 0.72−0.82; $P < .001$) as compared with men (HR = 0.88; 95% CI: 0.85−0.92; $P < .001$) (Fig. 80.4). There was a significant interaction between female sex and CRTD for the outcome of mortality. Among patients with LBBB and QRSd $\geq$ 130 ms, both women and men with CRTD had lower mortality risks compared with ICD recipients; however, the mortality difference associated with CRTD in patients with LBBB was greater in women (HR = 0.74; 95% CI: 0.68−0.81; $P < .001$) as compared with men (HR = 0.84; 95% CI: 0.79−0.89; $P < .001$) with a significant interaction between female sex and CRTD [26]. In patients without LBBB, CRTD was not associated with lower risk of death as compared with ICD. No differences between men and women in mortality risk were noted also in this group.

An additional study from this cohort of patients implanted with CRT [27] (n = 31,892, 11,542 women) confirmed that, among CRT-implanted patients, women had lower risk of death as compared with men (HR: 0.82;

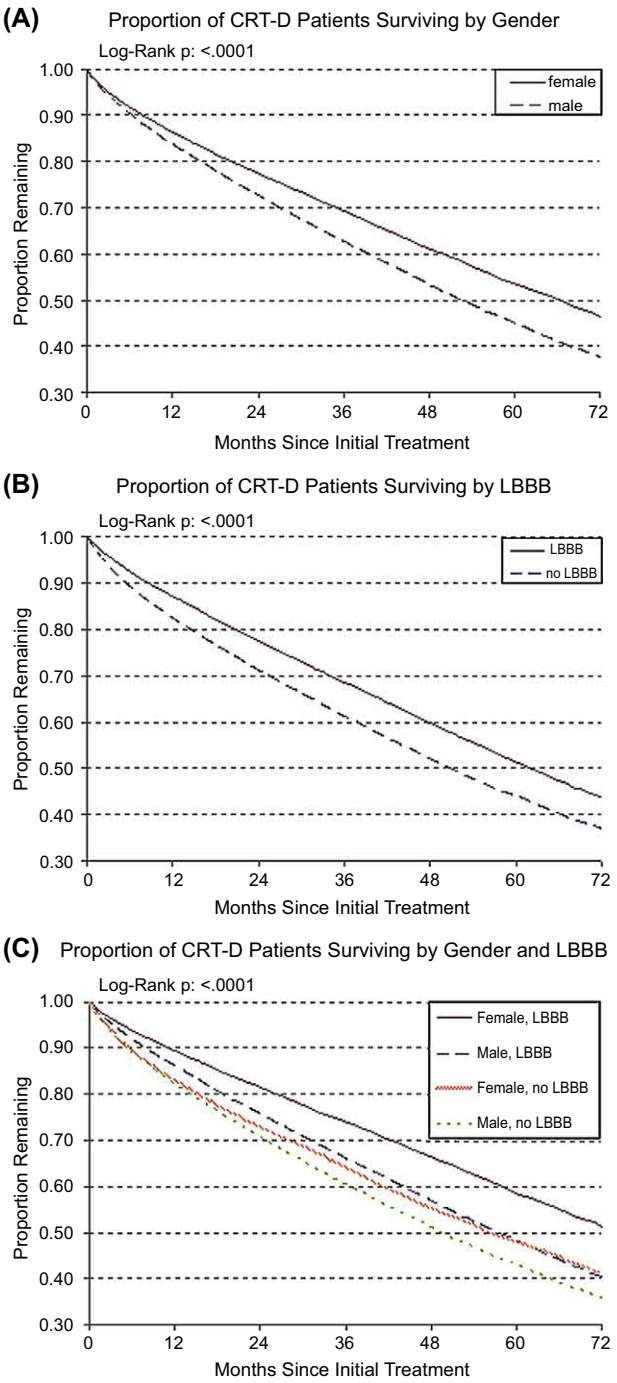

FIGURE 80.2 Kaplan–Meier plots of survival. Results are stratified according to (A) sex, (B) left bundle branch block (LBBB), or (C) both. Women had better survival than men, and LBBB patients had better survival than non-LBBB patients. *CRTsD*, cardiac resynchronization therapy defibrillators [25].

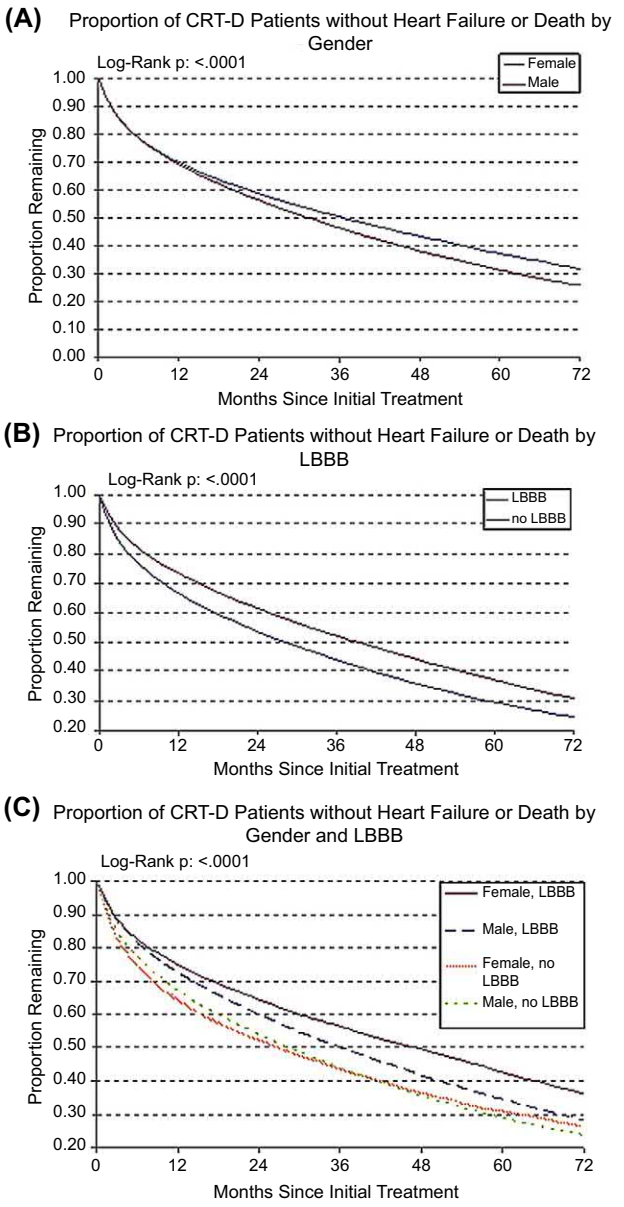

FIGURE 80.3 Kaplan–Meier plots of survival and freedom from HF hospitalization. Results are stratified according to (A) sex, (B) LBBB, or (C) both. Similar to analysis with death alone, women and LBBB patients had better survival free of heart failure (HF) hospitalization or death compared with men and non-LBBB patients, respectively. Abbreviations as in Fig. 80.2 [25].

95% CI: 0.78–0.87). However, this reduced risk of death was confined to patients with LBBB (HR: 0.79; 95% CI: 0.74–0.84) and not to CRT-implanted patients without LBBB (HR: 0.96; 95% CI: 0.86–1.06). Furthermore, as compared with patients with QRSd of 120–129 ms, reduced risk of death was seen in men as well as women with LBBB and QRS>140 ms without an interaction between QRSd and sex in these patients (Fig. 80.5). In contrast, in the non-LBBB population, mortality risk was similar regardless of QRS duration, and no sex-based differences in mortality risks were found (Fig. 80.5) [27]. Main findings of CRT in men and women are given in Box 80.1.

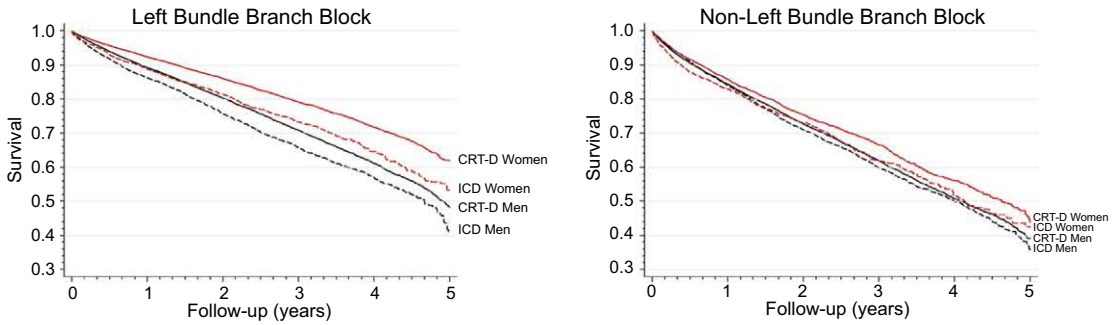

FIGURE 80.4 Propensity score—weighted Kaplan—Meier analysis of cardiac resynchronization therapy defibrillator (CRTD) versus implantable cardioverter defibrillator (ICD) by sex in left bundle branch block (LBBB) and non-LBBB. Curves indicate survival of CRTD (*solid lines*) versus ICD (*dashed lines*) in women (red) and men (black) after propensity score weighting in LBBB (left) and non-LBBB (right) [26].

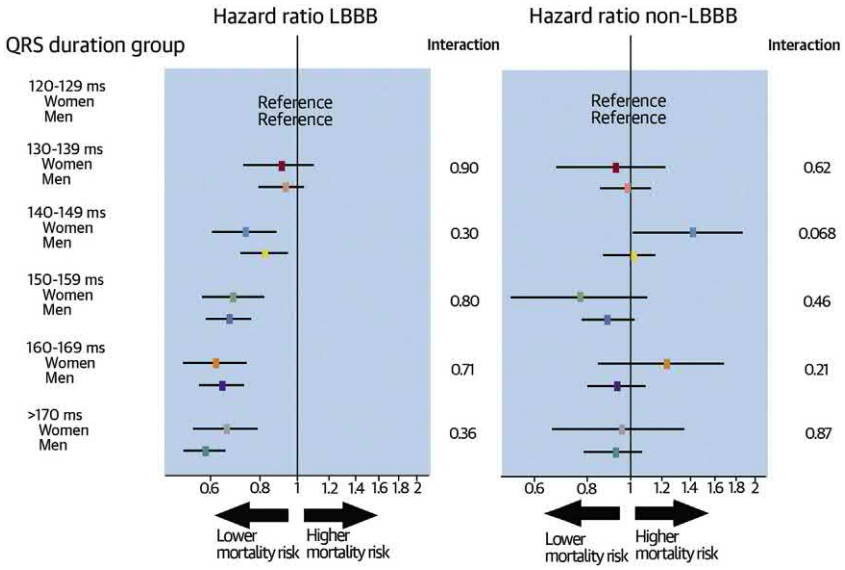

FIGURE 80.5 Multivariable hazard ratios for mortality in LBBB and non-LBBB QRS duration groups by sex. Points reflect hazard ratios for all-cause mortality in LBBB (left) and non-LBBB (right) in 10-ms QRS duration groups for women and men. Lines indicate 95% confidence bounds. Sex-by-treatment interaction probability values are reported for every QRS duration category [27]. *LBBB*, left bundle branch block.

BOX 80.1 Main points from observational studies

Women who underwent CRT have more commonly NICMP
Women have more often CLBBB in their baseline ECG
Women have QRSd 10—15 ms narrower than men, even with CLBBB
Women have better echocardiographic response to CRT than men. The response is not dependent on presence of QRSd >150 ms. Greater proportion of responders and superresponders among women.
QRSd threshold for CRT response and benefit may be lower in women with LBBB (135 ms) as compared with men (150 ms)
Women have lower risk of death and HF hospitalizations as compared with men after CRT
Lower risk of death in women is confined to LBBB patients but not to non-LBBB patients

Metaanalyses of cardiac resynchronization therapy in women versus men

Herz et al. [28] evaluated sex differences in enrollment criteria, baseline characteristics, and outcomes in articles specifically assessing CRT. In the 183 studies that reported the frequency of men and women—no differences in enrollment criteria were found for men and women [28]. Half of the studies included ≤35% women, and 90% of studies included ≤23% women of the total number of patients [28]. Most baseline characteristics were balanced between men and women except for a higher rate of ischemic CMP among men and higher rate of NICMP in women. No differences were noted between men and women in terms of NYHA FC improvement, but LVESV reduction of ≥15% was more common in women. The majority of the studies in their systematic review showed

greater benefit in terms of death and HF hospitalizations in women as compared with men [28].

Cheng et al. [29] conducted a metaanalysis of studies that evaluated the effect of CRT in men and women with HF and EF $\leq$ 35% and QRSd >120 ms. In this study, summary HRs (95% CI) were calculated by pooling the study-specific estimates using a random-effects model that included and accounted for between-study heterogeneity. They included observational cohort studies as well as randomized controlled trials. Their metaanalysis included 72 studies with 33,434 patients, of whom 24% were women, and 55% had an ischemic etiology. Women had more often LBBB and NICMP at baseline, whereas men had ischemic CMP more commonly [29]. In the pooled metaanalysis, women had 33% lower risk of death, 20% lower risk of death or heart failure, 41% lower risk of cardiac death, and 42% lower risk of HF as well as 41% lower risk of ventricular arrhythmia and sudden cardiac death [29]. No evidence of publication bias was noted with funnel-plot analysis or Egger and Begg tests. Although significant heterogeneity was observed among the 45 available studies (I2 = 29.49%; 95% CI: 0%−51.36%; $P = .03$), little of it was explained by study design ($P = .20$), percentage of women ($P = .64$), sample size ($P = .87$), number of events ($P = .55$), duration of follow-up ($P = .22$), average LVEF ($P = .70$), whether risk profiles were adjusted ($P = .53$), or whether patients with atrial fibrillation were enrolled ($P = .33$) [29].

Women had consistently greater improvements than men with CRT therapy in echocardiographic parameters representing reverse cardiac remodeling. They had greater reduction of their LVEDV (-22.68 ± 12.70 vs. -10.88 ± 7.24; $P < .001$), LVESV (-24.79 ± 9.73 vs. -13.47 ± 6.69; $P < .001$), and greater improvement in LVEF (9.42 ± 8.60 vs. 7.64 ± 8.32; $P < .00$). Absolute changes in functional parameters such as NYHA FC and 6-min walk test showed no significant difference between men and women [29].

Han et al. [30] conducted a metaanalysis of 58 studies involving 33,445 patients (23% of whom were women) from randomized controlled trials and from prospective or retrospective studies of patients with QRSd $\geq$ 120 ms and LVEF $\leq$ 35%, with follow-up periods > 6 months. Women had a lower risk of death after CRT as compared with men (HR: 0.67; 95% CI: 0.62−0.73, $P < .0001$); with no evidence of publication bias. Women had also a lower risk of HF hospitalizations (HR: 0.58; 95% CI: 0.46−0.74, $P < .0001$). Of note, significant interactions were found between death and presence of ischemic heart disease, which is more prevalent in men in this study and others. This may explain the increased risk of death in men after CRT implantation [30].

A patient level metaanalysis of three clinical trials comparing CRTD and ICD in patients with HF in NYHA FC II was conducted by Zustereel et al. [31]. These authors pooled individual patient data submitted to the FDA from the following trials: MADIT-CRT (the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy), RAFT, and REVERSE (Resynchronization Reverses Remodeling in Systolic left Ventricular Dysfunction Trial). In this metaanalysis, the authors compared the differences not only in outcomes between men and women but also in individual subgroups such as presence of LBBB and by QRS duration (QRS groups 120 to 129, 130 to 149, and 150 ms or longer). This analysis included 4076 patients of whom 52% had ischemic cardiomyopathy and 22% were women. Women had more frequently NICMP (67% vs. 33%) and LBBB at baseline (85% vs. 68%). Women had a greater reduction, as compared with men, in the risk of death or HF (by 60% vs. 26%) and death alone (by 55%vs. 15%). In patients without LBBB, no benefit with CRTD was seen as compared with ICD in both men and women [31]. Interaction analysis revealed that the efficacy of CRTD was significantly better in terms of death and death or HF in women with LBBB, QRS duration shorter than 150 ms, and NICMP. Specifically, within the LBBB groups, both men and women treated with CRTD showed reduction in death. However, men did not have any benefit from CRTD in patients with QRS <150 ms. In men with LBBB and QRS duration of 130−149 ms, CRTD did not have a significant effect on HF or death (HR: 0.85; 95% CI: 0.60−1.21) or death alone (HR: 0.86; 95% CI: 0.49−1.52). In contrast, women with LBBB and QRSd of 130−149 ms had a significantly lower risk of HF or death (HR: 0.24; 95% CI: 0.11−0.53) and of death alone (HR: 0.24; 95% CI: 0.06−0.89) with CRTD. Interaction analysis in LBBB with QRS of 130−149 ms revealed that the difference in treatment efficacy between women and men was significant for the end point of HF or death ($P = .003$) but not for death alone ($P = .10$). The authors concluded that women with LBBB had a significant benefit from CRTD even with QRS < 150 ms ($\geq$130 ms), whereas men with LBBB showed benefit at QRS of >150 ms.

An additional metaanalysis was performed by Yin et al. [32] of 11 observational trials that specifically performed a comparison of male and female sex in response to CRT (149,259 patients, 26% women). Women had a higher rate of NICMP (47% vs. 31%) and a lower rate of ischemic CMP (52% vs. 69%). This study showed that in women implanted with CRT, mortality was significantly lower as compared with men with CRT (OR: 0.50; 95% CI: 0.36−0.70). This observation was consistent even after removing a large study that included only patients with CRTD. No significant differences were observed between

men and women in terms of the degree of improvement in quality of life, 6-minute walk distance, and NYHA FC [32]. In terms of differences in EF improvement, most studies showed larger improvement in women, but one study did not. When taking into account all seven studies that reported the differences in EF, there were no differences between men and women (SMD 0.12; 95% CI: −0.14 to 0.39; I2 = 85.8%). However, after removing from analysis this single study that included exclusively patients with NICMP, there was a greater improvement in EF in women as compared with men (SMD 0.25; 95% CI: 0.07−0.43; I2 = 64.0%). LVEDD reduction during follow-up was significantly more pronounced in women as compared with men. No differences were noted between men and women in the small number of studies that reported change in LVESV and LVEDV over time [32]. Summary of the of observational studies comparing men and women with CRT are provided in Table 80.1. Table 80.2 provides summary of meta-analyses comparing men and women with CRT.

TABLE 80.1 Summary of observational trials.

Study	Design	Study patients	Main findings
Levya et al. [16]	Observational single center	550 patients, 22% women, 35% NICMP	Better echocardiographic response and functional improvement in women and lower risk of death and HF hospitalizations
Wang et al. [17]	Observational single center	512 patients ≥ 75, HF NYHA FC III–IV, 149 (29%) women	Lower mortality in women as compared with men
Varma et al. [18,19]	Observational single center	212 patients, nonischemic CMP, LBBB	Better improvement in women in EF, LVEDD, in LVESD. Improvement in men is better in QRSd>150 ms and independent of QRSd in women Association with QRSd disappears after correction to LV mass [19] QRSd threshold in women with CLBBB—135 ms
Cipriani et al. [20]	Observational two centers	507 patients, 20% women, 61% NICMP	Lower risk of death in women with NICMP only. Higher rate of responders in women. Echocardiographic improvement in women better than men
Zabarovskaja et al. [21]	Observational single center	619 patients, 119 women, 19%	Women had lower risk of death and HF hospitalizations
Barra et al. [22]	Observational single center	5307 patients, 22% women	Lower risk of death and cardiovascular death
Xu et al. [23]	Observational single center	728 patients; 166 women, 23%	Women had more symptomatic improvement in HF than men After adjusting for multiple favorable confounding variables that were more often seen in women, the survival and echocardiographic benefit from CRT was not significantly different between men and women
Levya et al. [24]	Electronic health records	50,048 patients; 12,257 women, 25%	Women had lower risk of death as compared with men
Loring et al. [25]	Medicare population	144,642 patients, 26% women	Women have lower rates of death. Female sex and LBBB are associated with lower risk of death. Lower risk of death in women with LBBB as compared with men with LBBB
Zustereel et al. [26,27]	NCDR ICD Registry	75,159 patients (4122 women, 32%) [26], 31,892 patients (11,542 women; 36%) [27]	Among patients implanted with CRT, women have lower risk of death, mainly observed in the LBBB group but not in non-LBBB patients

CLBBB, conventional left bundle branch block; *CRT*, cardiac resynchronization therapy; *EF*, ejection fraction; *FC*, functional class; *HF*, heart failure; *ICD*, implantable cardioverter defibrillator; *LBBB*, left bundle branch block; *LVEDD*, left ventricle end-diastolic diameter; *LVESD*, left ventricle end-systolic diameter; *NCDR*, National Cardiovascular Data Registry; *NICMP*, nonischemic cardiomyopathy; *NYHA*, New York Heart Association.

TABLE 80.2 Summary of main metaanalyses comparing men and women treated by CRT.

Study	Design	Study patients	Main findings
Herz et al. [28]	CRT studies that reported baseline characteristics (n = 183) and clinical outcomes (n = 100)	Traditional CRT criteria. Majority: LVEF ≤ 35%, NYHA FC III–IV, QRS > 130 ms	90% of studies included ≤23% women No differences in NYHA FC, greater number of responders in women—LVESV reduction, lower risk of death, and HF in women
Cheng et al. [29]	Cohort studies or randomized controlled studies that had a randomized design and estimate of the risk for specified endpoints for women compared with men, adjusted for all possible baseline confounders or covariates HRs (95% CI) were calculated by pooling the study-specific estimates using a random-effects model that included between-study heterogeneity	HF patients with LVEF ≤35% and QRS duration ≥120 ms 54.8% had an ischemic CMP and 24.1% were Women (n = 33,434)	Women's risk compared with men (HR, 95% CI): Death: 0.67 (0.61–0.74) Death or HF: 0.80 (0.71–0.90) Cardiac death or HF: 0.69 (0.56–0.85) Cardiac death: 0.59 (0.42–0.84) HF only: 0.58 (0.44–0.76)
Han et al. [30]	Randomized controlled trials and prospective or retrospective studies, follow-up periods > 6 months	QRSd > 120 ms and LVEF < 35% 58 studies 34,455 patients (51.39% ischemic, 23.08% women)	Women's risk compared with men (HR, 95% CI): All-cause death: 0.67 (0.62–0.73) HF or HF hospitalization: 0.58 (0.46–0.74)
Zustereel et al. [31]	Randomized trials comparing CRTD versus ICD Individual patient data from the study had been submitted to the FDA: 1. MADIT-CRT: the Multicenter automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy 2. RAFT: the Resynchronization–defibrillation for ambulatory Heart Failure Trial 3. REVERSE: Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction Trial	Patients with HF NYHA class II 4076 patients (50% ischemic cardiomyopathy, 878; 22% women)	- Women had a greater reduction in the risk of death and HF or death as compared with men with CRT - Benefit in men and women was seen in patients with LBBB but not in patients without LBBB - Men with LBBB showed benefit only with QRS duration >150 ms Women showed benefit with CRT with QRS duration >130 ms
Yin et al. [32]	11 observational trials of patients with CRT. 149,259 patients with CRT (26%) are women	Not sspecified. Traditional criteria for CRT	Women had lower risk of death as compared with men, greater improvement in EF

CMP, cardiomyopathy; *CRT*, cardiac resynchronization therapy; *CRTD*, CRT defibrillator.*EF*, ejection fraction; *FC*, functional class; *HF*, heart failure; *HR*, hazards ratio; *ICD*, implantable cardioverter defibrillator; *LBBB*, left bundle branch block; *LVEF*, left ventricle ejection fraction; *LVESV*, left ventricle end-systolic volume; *NYHA*, New York Heart Association.

Conclusions

There are multiple data that suggest that women derive more benefit from CRT therapy as compared with men. This is evident both by echocardiographic parameters of reverse remodeling (LVEDD, LVESV, EF) and in terms of mortality reduction and HF. Whether this is related to the effect of female sex by itself or to the higher prevalence of NICMP and LBBB and lower prevalence of ischemic CMP in women is not settled. Of note, women with LBBB derive benefit from CRTD with QRSd >130–135 ms, whereas this benefit is seen in men with LBBB and QRSd>150 ms. This point should be taken into consideration to ensure adequate access to therapy in women who currently do not meet class I indication for CRT (QRSd>150 ms).

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Chapter 81

Lead extraction in women

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Women have traditionally been underrepresented in clinical trials, and most of the available results have been extrapolated to the female population assuming identical results in men and women.

Even though the prevalence of cardiovascular disease in men and women is similar, use of cardiovascular procedures and devices is far higher in men [1]. In recent years, various studies have pointed a growing interest in the role of sex differences as a key determinant of safety outcomes in health care [2−4], and the crescent awareness of sex differences in access and response to arrhythmia therapies has led to the publication of a specific consensus document [5] endorsed by the European Heart Rhythm Association (EHRA).

Since lead extraction has become an integral part of cardiovascular implantable electronic device lead management, its impact on the female population seems to have interesting implications.

Characterization of sex-specific outcomes demands analysis of large data sets, but this is limited by the significant underrepresentation of women in randomized, clinical trials.

Transvenous lead extraction: the numbers

In recent years, the number of cardiac implantable electronic device (CIED) has been growing [6], with approximately 1.2−1.4 million CIEDs implanted annually worldwide [7], and differences in rates among women and men are observed, despite sex-neutral guidelines recommendations. For example, as recently reported by Ghare et al. [1], randomized controlled trials evaluating implantable cardioverter defibrillators (ICDs) include only 10%−30% female patients, partially because of the higher prevalence of heart failure with preserved ejection fraction in women. Moreover, ICDs are seen to be used more frequently in men (32.3 per 1,000, n = 65,917) for primary prevention compared with women (8.6 per 1,000, n = 70,504), even after consideration of the prevalence of heart failure with reduced ejection fraction [3].

The use of CIEDs has continued to rise along with indications for their removal: The number of CIED complications has steadily increased due to the growing of annual devices implantations, more complex devices and procedures, higher-risk patients, and lead malfunctions and recalls [8]. Transvenous lead extraction (TLE) is the gold standard in the treatment of CIED-related complications. An estimated 10,000−15,000 pacemakers and ICD leads are extracted annually worldwide using specialized tools and techniques [9]. Although infection has been the most common indication for device-assisted lead extraction, lead malfunction, abandoned and recalled leads have increased the number of extractions performed in recent years.

We know that once implanted, leads are held in place by scar tissue in the major veins and surrounding cardiac structures, making their withdrawal challenging. The degree of endothelial fibrosis is proportional to the length of time the lead has been implanted and patient's vascular inflammatory reactivity. Therefore, beside the primary indication, TLE remains a complex and technically challenging procedure that carries risk of significant adverse events, including vascular complications such as superior vena cava tear, myocardial avulsion, pericardial effusion, hemothorax, and death.

Indications for TLE can be grossly divided into infectious (a class I recommendation according to the most recent Heart Rhythm Society (HRS) document [7]) and noninfectious indications.

CIED infections have become increasingly prevalent because of the rise in CIED implantation, an aging population with multiple comorbidities [10]. Clinical presentation could be challenging; however, it is not uncommon for the patient to present with skin erosion or exposed decubitus (an example in Fig. 81.1). According to the recent European Lead Extraction ConTRolled registry (ELECTRa) study

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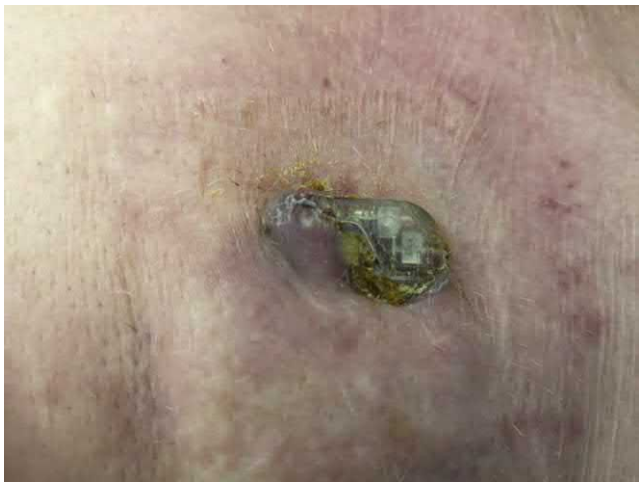

FIGURE 81.1 Skin erosion and exposed decubitus in a patient with CIED infection. *CIED*, cardiac implantable electronic device.

[11], infections make up 52.8% (19.3 systemic and 33.1% local) of the indications for lead extractions. Obviously, infected devices are associated with a high financial burden and significant rates of morbidity and mortality and require aggressive treatment.

If the action to take in front of an infection is clear, the decision to perform an extraction in some noninfectious scenarios requires a careful weighing up of the risk and long-term prognosis. In addition to lead malfunction, some important noninfectious indications for extraction include manufacturer recall, lead redundancy and required upgradings, or conditions as venous occlusion.

Transvenous lead extraction: the technique

The term *lead extraction* applies to pacemaker and ICD leads that have been implanted >1 year or that require special equipment to remove regardless of implant age [7]. Lead removals via an access other than the original venous insertion site are also defined extractions. *Lead explantation* is a procedure in which a lead is removed without specialized tools and all leads have been implanted for less than 1 year. In addition, procedural success for a lead extraction is defined by the removal of all targeted leads and lead material from the vascular space (*complete procedural success*) or retention of a small portion (<4 cm) that does not negatively affect the outcome goals of the procedure (*clinical procedural success*) [12]. On the other hand, *procedural failure* is defined as the inability to achieve either complete procedural or clinical success, or the development of any permanently disabling complication or procedural-related death.

The extraction technique has been largely described [13] with no distinction between sexes in the planning of the procedure. The vast majority of TLE procedures are performed from the lead venous entry site (Fig. 81.2): TLE is initially attempted by inserting a regular stylet to preserve the lead's lumen, disengaging the active fixation mechanism if possible, and applying steady traction with or without the use of a specialized locking stylet that stabilizes the lead.

If manual traction alone is unsuccessful, one or more tools may be necessary, including simple polypropylene telescoping sheaths (Fig. 81.3), rotating mechanical dilator sheaths, or powered sheaths. Alternatively, when the leads are intravascular and free-floating or the removal through the implant vein is not possible, a multiple venous approach (femoral and jugular vein, even combined) [14] can be applied.

In the past few years, the introduction of powered laser sheaths was probably one of the greatest changes in the lead extraction scenario [15,16]. The laser sheath applies circumferential pulses of energy at its distal end, dissolving tissue in contact with the tip of the sheath by photochemical destruction of molecular bonds and photothermal ablation that vaporizes water and rupture cells, with resultant photomechanical creation of kinetic energy.

Currently, there are no differences in TLE approach based on patient's sex; nevertheless, a series of considerations on the risk and complications related to the procedure should somehow influence our practice.

Complications and risk

Sex differences in acute complications of CIED implant have already been investigated [4]: The exact mechanisms for increase in complications among women remain unclear, but authors have suggested that they can be potentially explained by anatomical differences. As complication

FIGURE 81.2 Intraoperative moment: lead isolation from the initial insertion venous entry site.

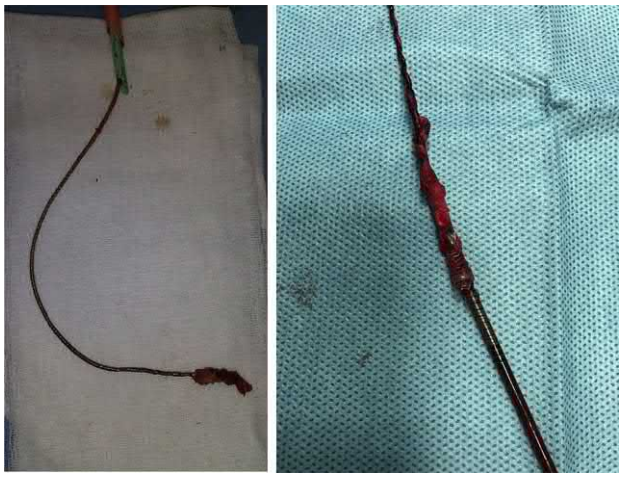

FIGURE 81.3 Example of removed lead with coarse fibrotic traces.

of implant procedures, women are twice as likely to require pleural drainage, probably because of thinner vessel walls, smaller vessel diameter, and/or less tissue between subclavian vein and pleura. Consistent with these findings, evidence exists to suggest higher rates of complications in women undergoing central venous catheterization [15].

Based on these observations, it is interesting to analyze in detail what happens to women who undergo TLE.

During the past decades, TLE techniques have improved, becoming a complete, safe, and effective procedure. Recently, the EHRA in 2018 [12] and the HRS in 2017 [7] published recommendations on TLE with well-defined definitions, allowing an accurate estimation of success and complication rates. However, serious complications that require emergent intervention may still arise in 0.2%−1.8% of cases in even the most experienced hands. There has, therefore, been a concerted effort to identify factors associated with complications to help clinicians in the decision-making process [16], and the main factors are listed inTable 81.1. Authors usually distinguish *major complications*, as any of the outcomes related to the procedure that is life threatening or results in death or requires significant surgical intervention (i.e., death, cardiac or vascular avulsion, pulmonary embolism, stroke), and *minor complications,* as any undesired event related to the procedure that requires medical intervention or minor procedural intervention to remedy (i.e., pericardial effusion, hemothorax, migrated lead fragment with without sequelae, pneumothorax).

The most important risk factors for major complications in TLE are the number of leads requiring removal, long implantation time, ICD lead, operator experience, and interestingly **female sex**. On the one hand, there are patient-related risk factors, such as age (young patients often show a massive fibrotic reaction), sex, and anatomy, which are by definition *nonmodifiable.* On the other hand, there are device-related factors, which are *modifiable* and may be controlled at the time of implantation [23].

In recent years, various risk stratification schemes were proposed to categorize patients as low, moderate, and high risk for lead extraction and to predict the difficulty of the extraction procedure. The lead extraction difficulty (LED) score proposed by Bontempi et al. [24] was defined as the number of extracted leads within a procedure + lead age (years from implant) + 1 if dual coil 1 if vegetation; this score independently predicts complex procedure at both univariate and multivariate analyses; notwithstanding, it does not consider female sex as a risk factor.

Although, in previous investigations, women were found to have more complications [7], the causes of the higher complication rate are not clear. As observed by Jachec et al. [25], men with CIED probably more often develop infectious complications, and TLE is performed earlier than in women, meaning that leads with shorter implant duration are extracted. The procedural risk related to the female sex was highlighted in a more structured way in ELETRa registry [11], as we are going to discuss in detail. The possible explanation for female sex as a risk factor is BMI $<25\ kg/m^2$ and thinner venous and myocardial wall.

In addition to acute complications, TLE procedures are potentially complicated by significant tricuspid valve (TV) injury with a subsequent increase in tricuspid regurgitation. This occurs when the extensive fibrotic adhesion between leads implanted on a long basis and between the lead and the TV apparatus is disrupted. As described by Park et al. [26], traumatic injury to the TV during TLE is more common in women and particularly with the use of tools such as laser sheath and snare. Whereas the tools used suggest the difficulty to TLE and the approximate degree of scar tissue ablation to remove the lead, women are more prone to complications during aggressive TLE. Use of the standard laser sheath seems to make extraction easier but is associated with a higher incidence of death and major complications [27].

Transvenous lead extraction: the registries and real world data

In the past 15 years, many reports of single- and multicenter TLE experiences were published, but data about safety and efficacy supported by large studies were lacking. Two large multicenter prospective trials independent from industry observational studies of consecutive TLE procedures have been recently performed both in Europe and in North America: the *ELECTRa* and the *LExICon* registries, summarized in Table 81.2.

The ELECTRa [11] is the largest prospective registry of consecutive TLE procedures conducted by the EHRA, with

TABLE 81.1 Factors associated with higher TLE procedural risk. *TLE*, transvenous lead extraction.

Factor	Criteria	Comments
Body mass index	<25 kg/m^2	Related more to size than sex [17,18]
Sex	Female	Complications higher in women compared with men [7]
Congenital heart disease	Complex anatomy	Size, tortuous lead routes, shunts
Comorbidities	Age, poor LV function, renal failure, coagulopathy, large vegetations	Most of the risk is periprocedural [18,19]
Venous status	Occluded or severely stenosed	Higher risk with greater lead cross-sectional area in the young. Limited access for additional procedures [20]
Number of leads	Greater number of leads present or extracted	More lead–lead and lead–tissue interactions [17]
Implantation time	Greater than 1 year, rising further thereafter	Time-dependent tissue reaction to leads [17,19]
Fixation mechanism	Passive	Active fixation easier to extract [21]
Lead body geometry	Nonisodiametric	Catching on bridging tissues [21]
ICD lead	Coil complexity	Greater diameter, fibrous ingrowth into coils [21]
Special/damaged leads	Design/provoked deficiencies	Notable examples: Riata [22], starfix, accufix
Volume's center	<30 extraction procedure/year	Increased incidence of complications [7]
Operator's center	<300 extraction procedure performed	Increased incidence of complications [17]
Tools, technique, approaches	Extraction outcomes and complications	Femoral approach, and powered sheaths increase complications, internal jugular approach increase outcomes [14]

Adapted from Deharo JC, et al. Pathways for training and accreditation for transvenous lead extraction: a European Heart Rhythm Association position paper. Europace. 2011;14(1):124–134. https://doi.org/10.1093/europace/eur338.

TABLE 81.2 Large published works in lead extraction and complications.

	ELECTRa [11]	LExICon [27]
Patients characteristics		
Patients, n	3555	1449
Age, years	66.8 ± 15.6	63.4 ± 17.1
Male, n (%)	2566 (72.2)	1041 (71.8)
Ejection fraction, %	45.5 ± 14.7	37.7 ± 16.6
Coronary artery disease, n (%)	1396 (39.6)	728 (50.2)
Diabetes mellitus, n (%)	782 (22.1)	403 (28.1)
Indication for extraction		
Infection, n (%)	1872 (52.8)	825 (56.9)
Lead malfunction or abandoned	1439 (40.4)	547 (37.7)
Procedural data		
Technique	Traction, locking stylets, mechanical and powered sheaths	Laser
Number of leads	6493	2405
Complete procedural success (%)	95.7	96.5
Major complications (%)	1.7	1.4
Procedural mortality (%)	0.5	0.3

the specific aim to identify safety and efficacy of the current practice of TLE. The registry enrolled, from November 2012 to May 2014, a total of 3555 consecutive patients who underwent TLE at 73 centers in 19 European countries; a total of 6493 leads were targeted for extraction.

The primary endpoint was TLE safety defined by predischarge major procedure-related complications including death. Secondary endpoints included clinical and radiological success and overall complication rates. A total of 3510 patients (72.2% male) underwent TLE, with a procedure-related major complication rate of 1.7% (58 patients) and a mortality of 0.5% (17 patients). The first important observation of the ELECTRa Registry was that infections were slightly more frequent (amounting to 52.8%) than noninfective indications (38.1% of cases) for TLE. Preliminary analysis showed that the 1-year mortality rate was 15.1% in patients with systemic infection, 6.9% in patients with a more local infection, and 3.0% in patients without infection.

Let' us see in detail the procedure related major complications (Fig. 81.4) and factors associated with clinical failure (Fig. 81.5).

In the subanalysis, authors observed that procedure-related major complication and deaths were more common in **female patients** (OR: 2.11; 95% CI: 1.23−3.62; $P = .0067$), leads with a dwelling time >10 years (OR: 3.54), with the use of powered sheaths (OR: 2.4) and a femoral approach (OR: 3.60). Furthermore, predictors of clinical failure included low volume centers (OR: 2.23), **female sex** (OR: 1.81), three or more leads targeted for extraction (OR: 2.47), a lead dwelling time >10 years (OR: 4.0), the use of powered sheaths (OR: 1.89), and a femoral approach (OR: 3.93).

A possible explanation for the sex-associated difference in outcome may be related to the fact that women have smaller and more fragile vessels that are more vulnerable to damage. In this regard, Zucchelli et al. [28] have recently described outcomes and predictors of cardiac avulsion or tear with tamponade and vascular avulsion after TLE, which are the most frightening complications [29]. Considering the ELECTRa Registry population, cardiovascular complications were more often observed in **females** ($P = .0082$), thrombosis or stenosis of superior venous axis ($P = .0087$), longer median dwelling time ($P < .0001$), passive fixation ($P = .0226$), and unipolar leads ($P < .0001$). More in detail, male patients (OR: 0.38, 95% CI: 0.18−0.83; $P = .0148$) had a lower likelihood of cardiac avulsion or tear with tamponade, even at multivariate analysis.

In their analysis, Zucchelli et al. suggested that the risk associated with females is partially determined by associated low body mass index and a higher frailty of this subgroup compared with males.

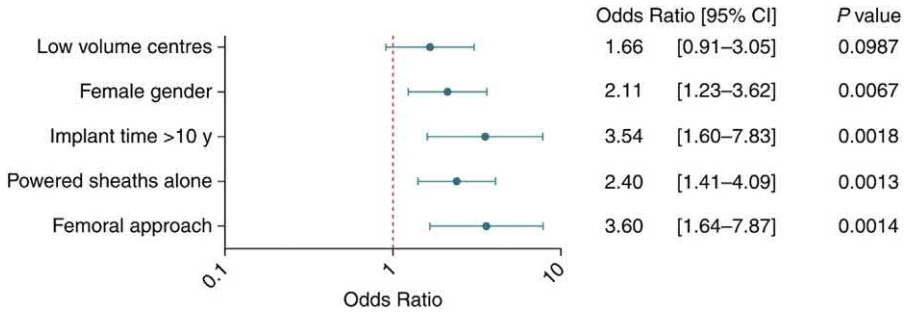

FIGURE 81.4 Procedure-related major complications (including death). *Modified from Bongiorni MG, Kennergren C, Butter C, et al. The European Lead Extraction ConTRolled (ELECTRa) study: a European Heart Rhythm Association (EHRA) registry of transvenous lead extraction outcomes. Eur Heart J 2017;38(40):2995–3005. https://doi.org/10.1093/eurheartj/ehx080.*

There are more considerations derived by a careful analysis of the data provided by the registry.

If in patients with CIED infections, the complete removal of all hardware is mandatory [7] and TLE is strongly recommended, the extraction of noninfected leads remains controversial and debated [30]. The decision to extract or abandon an unnecessary noninfected lead is multifactorial and should consider many procedural TLE complexities. Segreti et al. [31] showed that previously abandoned leads at the time of TLE were associated with increased procedural complexity, procedural failure, and major complication and may be associated with higher mortality. Univariate and multivariate analysis considered a large variety of parameters influencing the outcome, but no difference sex-related was observed.

In 2010, another large multicenter prospective observational study was conducted in the United States and Canada [16,27]. The aim of the study was to examine the safety and efficacy of laser-assisted lead extraction along with indications, outcomes, and risk factors in a series of 1449 consecutive patients enrolled from January and December 2007. In addition, the most common indication for extraction was infection (57% of total with a 29% of systemic infections and 27% of pocket infections). Clinical success was achieved in 97.7% of patients, and interestingly, the multivariate model indicated that failure to achieve clinical success was associated with patient BMI <25 kg/m^2. More precisely, when BMI was 25 kg/m^2, it predicted procedural major adverse events and clinical failure, whereas renal insufficiency, diabetes, BMI <25 kg/m^2, and presence of pocket infection were all independent predictors of all-cause in-hospital mortality. In contrast with Byrd et al. [17], Wazni et al. [18] found no association between sex and adverse events directly related to lead extraction, but this result could be influenced by the design on the study itself.

Other interest analysis is provided by the National Cardiovascular Data Registry (NCDR) ICD Registry, which reports data on implantation, complications, and in-hospital outcomes for ICDs across a wide spectrum of hospital in the United States. In this analysis of 11,304 real-world extractions, a complication rate of 2.3% and a mortality rate of 0.9% were found. The overall rate of major complications and intraprocedural mortality was similar to that of previously published data, and Sood et al. [9] describe **female sex** (OR: 1.35), admission for heart failure, and warfarin use as univariate predictors of increased risk of major complications in TLE.

As you can see, data are still confusing but suggestive of the need to pay more attention when we treat female patients, as we are getting used to do in other fields.

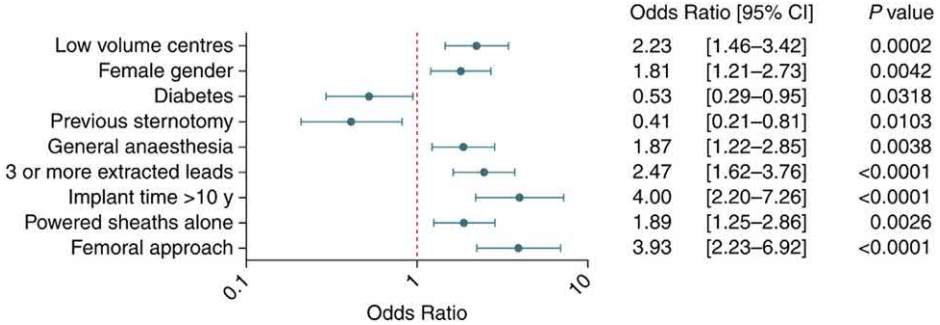

FIGURE 81.5 Procedure-related clinical failure. *Modified from Bongiorni MG, Kennergren C, Butter C, et al. The European lead extraction ConTRolled (ELECTRa) study: a European heart Rhythm association (EHRA) registry of transvenous lead extraction outcomes. Eur Heart J. 2017;38(40):2995–3005. https://doi.org/10.1093/eurheartj/ehx080.*

Conclusion

Expanding indications for CIEDs have led to an increasing number of implanted leads, and increasing patient comorbidities and increased life expectancy contribute to the increased need for lead extraction. TLE has established as the gold standard in the treatment of CIED-related infective complications and is often required in the management of lead malfunction.

TLE complications may be observed during or after the procedures with various levels of severity. Vascular damage, cardiac tamponade, and pulmonary embolism are only the most common described complications and, if not managed, potentially fatal in women, as well as in men. Whether women gain similar benefits to men implanted with pacemakers, ICDs, and cardiac resynchronization therapy, it' is pivotal to remind that female sex is a risk factor for major complications in lead extraction and that women are more prone to complications both for thinner cardiovascular walls and for a global frailty related to sex.

At present, the best way to reduce complications and increase safety is extracting the right patient, in experienced centers by trained operators, using appropriate techniques.

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Chapter 82

Quality of life with implanted devices

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Background

Over the past 20 years, quality of life (QoL) has been increasingly accepted as an important outcome measure in therapy including device therapy. QoL has been defined by the World Health Organization (WHO) as a state of complete physical, mental, and social well-being and psychological health and not merely the absence of disease or an infirmity. Most QoL forms include the patients' perception of performance in four broad domains, i.e., physical functioning, social interaction, psychological state, and somatic sensation [1].

Instruments of quality of life and their use in device studies

Instruments of QoL most often include the combination of a generic instrument measuring general QoL such as the EuroQual [2] or the SF 36 [3] and a disease specific developed to reflect the symptoms of a particular disease state like. For example, the Minnesota living with heart failure (HF) questionnaire [4] was developed for HF patients. For devices such as pacemaker therapy, there are at least two instruments. The Karolinska QoL questionnaire encompasses both general and disease-specific questions [5]. The Dutch Aquarel is a validated disease-specific questionnaire, which was developed to study patients with antibradycardia pacing [6].

The Karolinska questionnaire has also been utilized in studies on device studies in cardiomyopathies such as the pacing in cardiomyopathy (PIC) trial [7] studying short atrioventricular (AV)-delay AV-sequential pacing in hypertrophic cardiomyopathy and in the MUSTIC study on cardiac resynchronization therapy (CRT) in moderately severe HF patients [8]. Both trials were crossover randomized controlled followed by longer-term follow-up in active pacing.

In the later years, CRT trials comparing CRT to CRT off or implantable cardioverter defibrillator (ICD) therapy with a parallel study design the Minnesota [4] or the Kansas City Cardiomyopathy quality (KCCQ) of questionnaire have been used. The KCCQ is more sensitive than the Minnesota, in particular in mild HF [9].

The importance of using randomized controlled studies to detect differences in quality of life in device patients

It was commonly believed that the placebo effect was most common in drug studies. But a placebo effect of pacemaker therapy was also reported in the PIC trial [10,11]. In this crossover study that compared active to inactive short AV-delay AV-sequential pacing, there were significant improvements in some QoL dimensions also during the inactive pacing phase although significantly greater improvements in all areas of QoL were achieved during AV-sequential pacing. These improvements emphasize the placebo effect of device implantation, which is now widely recognized, meaning that there is no possibility to prove a benefit of a given therapy including device therapy *without a control group*. Sadly, the PIC study did not analyze QoL with respect to sex.

Women and men and quality of life in different populations without device therapy

In spite of QoL instruments used since the late 1980s to study the effects of cardiac pacing, the sex and gender differences were not highlighted until recently. Nowadays, sex and gender differences are in focus, emphasizing a greater awareness of potential QoL differences both at baseline and after an intervention such as device implantation.

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From the normal population, it is known that female sex and high age is associated with worse QoL when measured by EQ-5D-3L [12–14]. In HF studies, one recent study found that women with HF with preserved ejection fraction (HFpEF) patients expressed worse general QoL independent of age and HF severity than men with regard to all five dimensions of EQ-5D-3L part 1 [15]. Women expressed numerically more difficulties with statistical significance for mobility, usual activities, and anxiety/depression. Similarily women rated the global QoL question the EQ-VAS lower than men. But in spite of the fact that women with HFpEF expressed worse general QoL than men, there were no differences in the Minnesota Living with HF questionnaire in this epidemiologic study. In general QoL, the association with HF severity and outcome were more pronounced in men indicating that poor QoL might be more multifactorial and complex in women and thus potentially more difficult to treat.

In a recent study of QoL in patients referred for ablation due to paroxysmal supraventricular tachyarrhythmia [16], women had a significantly longer history of symptomatic arrhythmia before ablation compared with men. Physicians more often incorrectly interpreted women's symptoms as anxiety, stress, panic attacks, or depression compared with men, delaying referral for ablation. This may mean that women's' symptoms are not fully recognized as potentially disease related but more often connected to perceived psychological disorders. At baseline, women in this study had a higher symptom score, but 6 months after ablation, women were still more symptomatic, and their QoL improved less than in men, again suggesting that QoL in women may be more multifactorial.

Quality of life in device studies

The most important antibradycardia pacing studies comparing various modes of pacing in most cases included QoL assessments but only rarely encompassed analysis with regard to sex.

Large randomized controlled studies (Table 82.1)

QoL has been reported to improve in patients following pacemaker implantation for symptomatic bradycardia. Importantly, not all pivotal pacing trials included QoL results. In the Canadian Trial of Physiologic Pacing (CTOPP), there were no sex differences in QoL [17]. In the MOde Selection Trial (MOST) in sinus node dysfunction, men reported better QoL scores and improved functional status compared with women [18].The UK-PACE [19] in patients with high degree AV block or the DANPACE trial in patients with sinus node disease did not report QoL [20].

From a long-term QoL study focusing on pacemaker patients, Udo et al. reported long-term results as part of the FOLLOWPACE study [21]. Patients were assessed with SF 36, combined with the Aquarel QoL questionnaire and with a 7.5-year observation period. Of 1067 patients, 59% were male. The reason for pacing was high-degree AV block in 41% and sinus node disease or bradycardia in 35%, atrial fibrillation with slow ventricular rhythm in 18%, and other reasons in the remaining 6%. Dual-chamber pacing was given in 76%. The overall SF 36 score improved after pacemaker implantation, and although scores declined over time, values remained improved compared with preimplantation values. For all subscales, the highest value was seen after 1 year. For the disease-specific Aquarel QoL form, the most prominent improvement was for arrhythmia-related symptoms with most symptom scores remaining improved and with a sustained effect over time (Fig. 82.1). Female sex was associated with overall worse QoL (Table 82.2) as well as worse score for the disease-specific Aquarel subscales, in particular with regard to dyspnea. Presence of HF, diabetes, and hypertension also contributed to worse QoL with regard to the SF 36. Pacemaker mode, however, did not impact QoL in line with previous observation from large studies such as the MOST and CTOPP studies. In summary, the study demonstrated that the improvements in SF 36 following pacemaker implantation gradually declined over time; however, the increased (improved) scores on the role of physical functioning and mental health scores were maintained as well as improvements in chest discomfort or dyspnea as measured by the Aquarel questionnaire. The persistence in improvement strongly suggests effects by the pacemakers that go beyond placebo effects.

Recently, a study from the Swedish Pacemaker and ICD Registry studied QoL in ICD recipients with a treatment duration of at least 1 year [22]. A total of 2658 ICD recipients with a mean age of 65 years and 21% females were invited to answer a questionnaire on QoL based on EuroQual. Patients were on the average 65 years of age, 20.6% were female, and the mean ICD treatment duration was 4.7 years. A total of 35% were treated with a primary preventive ICD. Worse QoL was associated with greater number of comorbidities burden, female sex, a history of ICD shock, negative ICD experience, higher levels of ICD-related concerns, and the presence of anxiety, depression, or type D personality. No separate sex-specific information as to various dimensions of QoL was reported.

In an additional cross-sectional study including 990 patients who received an ICD following cardiac arrest, a questionnaire was completed with regard to comorbidities, EurQual 5D SL, HADS forms, and ICD concerns [23], EuroQual was compared with a sex- and age-matched Swedish population. The cardiac arrest survivors reported better EuroQual QoL index and less pain/discomfort

TABLE 82.1 Sex and cardiovascular outcomes in the major randomized clinical trials of pacing mode.

Study	Design	Females, %	Age, years	Quality of life results
CTOPP [17]	Ventricular versus physiologic pacing in patients with symptomatic bradycardia	1057 (41%)	73 ± 10	Using SF 36, improvements in QoL were reached in both women and men and with no difference between pacing modes
MOST [18]	DDDR versus VVIR in patients with symptomatic bradycardia secondary to SND	955 (47.5%)	74 (IQR: 67 −80 years)	Using SF 36, improvements in QoL were reached with no difference between pacing modes, and no analysis with regard to sex was made
UKPACE [19]	VVI versus VVIR versus DDD pacing in symptomatic bradycardia secondary to AV block	870 (43.0%)	80 ± 6	Did not report QoL
DANPACE [20]	AAIR versus DDDR in patients with symptomatic bradycardia secondary to SND	913 (64.5%)	73 ± 11	Did not report QoL

AV, atrioventricular; *IQR*, interquartile range; *QoL*, quality of life; *SND*, sinus node dysfunction.

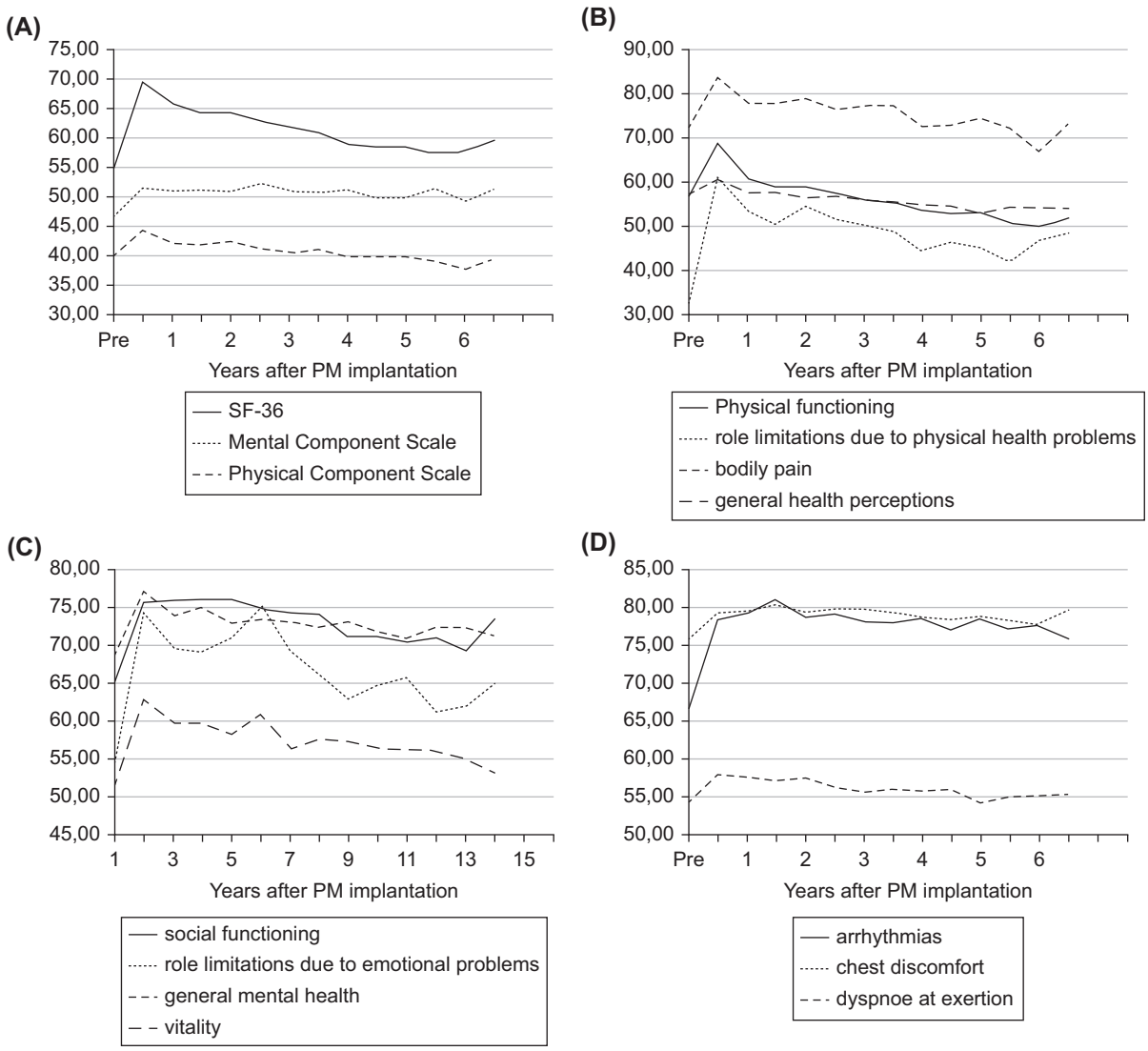

FIGURE 82.1 Estimated quality of life during long-term follow-up after first bradycardia pacemaker implantation, corrected for age, gender, diabetes, hypertension, heart failure, maintained AV synchrony, and cardiovascular disease. Panel A: Overall quality of life SF scores and mental and physical scores. Panels B and C: SF 36 subscales. Panel D: Disease-specific Aquarel scales. *From Udo EO, Van Hemel NM, Zuithoff NPA, Nijboer H, Taks W, Doevendans PA, Moons KGM. Long term quality of life in patients with bradycardia pacemaker implantation. Int J Cardiol 2013;168:2159–63.*

compared with the general population ($P < .001$). In contrast, they had more problems in mobility and usual activities ($P < .01$). Problems with anxiety and depression were reported by 15.5% and 7.4%, respectively. Being unemployed, having more comorbidities, perceiving less control, and having a type D personality were independently associated with all aspects of worse QoL. Furthermore, being female and suffering ICD-related concerns were independently associated with worse QoL in the regression models.

In a recent ICD study, SF 36 was reported separately in women and men in the intrinsic right ventricle trial [24]. Of a total of 1530 patients, 19% were females. Female patients (Fig. 82.2) scored statistically lower QoL than men for the SF 36 subscales for physical functioning (11 points), role physical (10.5 points), and vitality (10.4 points), and role emotional (15.2 points) functioning was severely depressed in women at baseline. Following ICD implantation, significant improvements were observed in all SF 36 subscales compared with baseline. Women improved to the same extent as men following ICD implantation. In addition, in an overview of 40 articles on ICD therapy, women and young patients had greater problems with body image following ICD implantation than men [25]. More attention to surgical techniques could improve QoL in women and younger.

TABLE 82.2 Regression coefficients (with 95% confidence intervals) for determinants of quality of life measured with overall SF 36 and the pacemaker specific Aquarel questionnaire.

	SF 36		Aquarel					
	Overall SF 36		Chest discomfort subscale		Dyspnea subscale		Arrhythmia subscale	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Female gender	−61 (−8.3 to −3.9)	<.0001	−1.6 (−2.9 to −0.4)	.0078	−26 (−3.8 to −1.4)	<.0001	−7.1 (−9.1 to −5.1)	<.0001
Age (per 10 years increase)	−4.0 (−5.0 to −3.0)	<.0001	0.0 (−1.0 to 0.0)	.5773	−1.0 (−2.0 to −1.0)	<.0001	1.0 (0.0 to 1.0)	.2644
Diabetes	−4.9 (−7.8 to −1.9)	.0014	−0 9 (−2.6 to 0.9)	.3488	−2.0 (−3.7 to −0.4)	.0170	−2.9 (−6.0 to 0.2)	.0639
Hypertension	−2.8 (−5.2 to −0.4)	.0212	−1.5 (−2.8 to −0.3)	.0162	−22 (−3.4 to −0.9)	.0008	−3.3 (−5.4 to −1.2)	.0022
Heart failure	−3.8 (−7.5 to −0.1)	.0459	−0.4 (−2.3 to 1.5)	.6829	−2.6 (−4.7 to −0.5)	.0162	1.7 (−1.3 to 4.8)	.2653
Cardiovascular disease	−3.4 (−5.7 to −1.2)	.0032	−2.1 (−3.3 to −0.9)	.0006	−2.1 (−3.3 to −0.9)	.0010	−3.1 (−5.1 to −1.0)	.0029
Maintained AV synchrony (AAI/DDD)	0.6 (−2.2 to 3.4)	.6860	−0.1 (−1.5 to 1.4)	.9443	0.6 (−0.8 to 2.0)	.3955	1.7 (−0.8 to 4.1)	.1776

AV, atrioventricular; *CI*, confidence interval.
Udo EO, Van Hemel NM, Zuithoff NPA, Nijboer H, Taks W, Doevendans PA, Moons KGM. Long term quality of life in patients with bradycardia pacemaker implantation. Int J Cardiol 2013;168:2159−63, with permission.

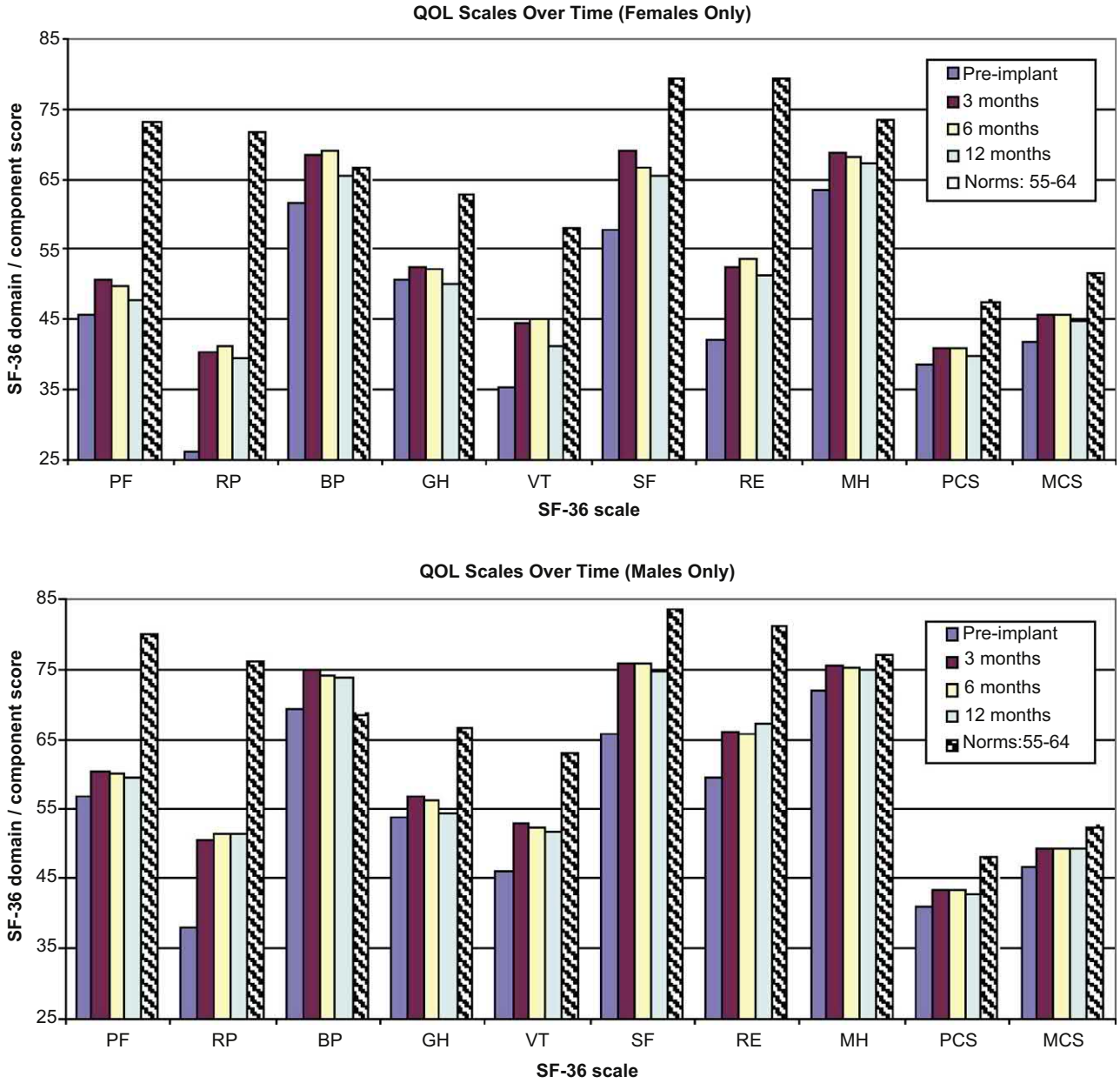

FIGURE 82.2 SF 36 quality of life subscale results in **women** (upper panel) and **men** (lower panel) ICD recipients at baseline and 3, 6, and 12 months following ICD implantation. Normative values of US population of 55−64 years old are shown for comparison [21]. *BP*, bodily pain; *GH*, general health; *ICD*, implantable cardioverter defibrillator; *MCS*, mental component score; *MH*, mental health; *PCS*, physical component score; *PF*, physical functioning; *RE*, role emotional; *RP*, role physical; *SF*, social functioning; *VT*, vitality. *From Udo EO, Van Hemel NM, Zuithoff NPA, Nijboer H, Taks W, Doevendans PA, Moons KGM. Long term quality of life in patients with bradycardia pacemaker implantation. Int J Cardiol 2013;168:2159−63; From J Card Eelectrophysiol 2017; 48:291−8 with permission.*

Reasons for differences in quality of life between women and men

Whether QoL differences are related to sex or gender remains a difficult question. Women undoubtedly may have a greater tolerance by society to express anxiety and depression, which then is explained by gender. Females may be more sensitive to expectations of physical beauty than men and hence more worried by changes in physical appearance such as caused by device implantation. But younger men most probably have similar perceptions and expectations. The menstrual cycle may influence psychological state, which has been highlighted in the premenstrual syndrome. Women also have smaller body size and

heart dimensions, which may be related to different perception of heart rhythm and disturbances. Both menopause and andropause moreover may be related to QoL changes. It goes beyond the scope of this chapter to explain the reasons for differences in QoL in device patients more in detail.

Conclusion

QoL is an important outcome measure, which is generally measured by a combination of a general QoL instrument and a disease specific. Although used in device studies, QoL results have rarely been reported with respect to sex. QoL assessments with respect to sex are more available in ICD recipients than in patients paced for bradyarrhythmia. Women overall seem to suffer more from anxiety and depression especially before device implantation. In ICD studies, women are reported to have worse QoL than men. In future studies, QoL should be measured with respect to sex to recognize and treat patients according to individual needs.

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Part XVIII

Outlook

Chapter 83

Obstacles for enrollment of women in clinical trials

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Introduction

Women were first excluded from clinical trials (CTs) following the disasters linked to the prescription of thalidomide or diethylstilbestrol in pregnant women in the 1960s [1,2]. The exclusion of women then worsened over the years, based on arguments such as the difficulty and cost of conducting mixed-sex trials where the hormonal status of women could lead to heterogeneous results [1,3,4]. Since regulations from the National Institutes of Health (NIH) were put in place in 1993 in the United States [5], the situation seems to have overall improved, but women are still underrepresented, especially in studies of cardiovascular (CV) diseases as well as in trials involving high-risk interventions [6–8]. Reasons for the underrepresentation of women in CV clinical trials are in part directly correlated to female sex (disease development at an older age [9–13], limited willingness to participate in CT involving high-risk interventions [6–8]), whereas others stem from a long history of CV research and body of evidence predominantly based on male subjects. The reasons for this male preponderance are the easy access to identifiable and convenient cohorts such as veterans or army recruits [1,4] and physicians' perception that women suffer less from CV diseases or are less at need for specialist consultation or interventions [11,14]. Electrophysiology (EP) CT is therefore particularly susceptible to underenrollment of female participants since some arrhythmias develop later in life in women and since EP is a particularly invasive specialty [6–8,15,16]. Improving patients' and physicians' education [6,11,17] and recruitment strategies[6] and adapting editors' and publishers' requirements [6,18] are the first steps to improve adequate representation of women in CT, which really reflects their prevalence in the diseased population.

Historical overview

The beginning of women's exclusion: pharmacological disasters

Two major pharmacological disasters, which took place in the 1960s, led to the first important exclusion of women from clinicals: first, the malformations caused in newborns by a widely used sleep aid, thalidomide, and second, the high incidence of genital cancer in children from mothers who used diethylstilbestrol to prevent complications in pregnancy [1,3,19]. Both these catastrophes incited the Food and Drug Administration (FDA) to introduce in 1977 the "General Considerations for the Clinical Evaluation of Drugs" [20], a document limiting the participation of women of childbearing potential in CT until drug teratogenicity could be excluded with certainty [1,21].

Further assumptions leading to women's exclusion from clinical trial

Further sex-associated factors led to the exclusion of women in the history of clinical research. First, there was the widespread belief that fluctuating women's hormone cycles would confound the results. It was therefore thought that including women would increase the trial costs and complexity of interpreting the results [1,3]. Second, the perception that women were not as likely as men to contract diseases was also extensively common. During the AIDS crises of the 1980s, for instance, women were considered as "vessels and vectors," and trials were focused on the male population [1]. CV trials were also major victims of these preconceptions, as shown by two large government-funded multimillion multidecade clinical trials studying coronary artery disease (CAD), the

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Multiple Risk Factor Intervention Trial [22], and the Physician's Health Study [23], which entirely excluded women [1].

First reactions to the underenrollment of women in clinical trials

The first reactions to the underenrollment of women in CT came from US regulatory bodies, first, due to the growing appreciation of the differences in pathophysiology, presentation, treatment, and outcome of several diseases in women and, second, due to the observation that less information about treatment was available for females [4,8]. In 1985, the Public Health Service Task Force on Women's Health Issues advised to pay more attention to women's health in CTs and led to the establishment of the first federally funded US organization attempting to counteract low women's enrollment rates, namely, the National Institutes of Health (NIH Office of Research on Women's Health (ORWH). This Office integrated women's health research as part of the NIH research agenda in 1990 [8,12]. In 1993, the NIH issued its Revitalization Act [5], which required the inclusion of women in every clinical trial involving a disorder that affects women [1,8,10,14,24]. The goal of this Act was to "ensure that the trial is designed and carried out in man sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women and men differently" [5,25]. This Act led to the institution of the Office of Women's Health (OWH) of the FDA, established in the United States by Congressional mandate, which aimed at the promotion of women's inclusion in CT and at the implementation of guidelines for sex-specific inclusion and data analysis [1,3,8,25,26].

In Europe, the International Council for Harmonisation (ICH) began addressing sex disparities during the 1990s by developing new regulatory standards addressing similar issues as the ones tackled by the NIH [2]: the representativeness of the target patient population and the conduction of analyses with respect to sex [27].

However, none of these authorities required specific proportions of women or separate sample size calculations for both sexes [10,25].

Contemporary situation

Impact of the regulatory dispositions

Whether or not the legal and regulatory dispositions formulated by the NIH in the United States or by the ICH in Europe really resulted in an increase of the number of women enrolled in clinical trials is debated [2,8,26]. While an improvement in women's enrollment has been observed since the 1980s [25,28,29], the trend predated any mandate and seemed to be due to the growing appreciation of important biologic differences between men and women and the demand of women for greater autonomy [8,30].

In 2009, an inclusion report from the NIH indicated that clinical research enrollees were 57.1% female (51.8% in non−sex-specific studies), demonstrating the success of their measures [31]. However, as highlighted in 2015 in the United States by the Government Accountability Office (GAO) [32], discerning whether all NIH institutes meet inclusion requirement is difficult, as they are aggregated in the reports [26].

A second aim of the regulations was to target sex-specific reporting [5,25]. The observed improvement in the communication of sex-related results is disappointing. Reviews of publications stemming from NIH trials between 1993 and 2015 consistently identified about one-third of manuscripts as reporting sex-specific results, with no significant improvement [12,25,26,28].

Attempts to assess the changes in women's enrollment in CTs, in general, over the past years remain difficult, as their evolution strongly depends on the field investigated [30], the type (governmentally sponsored or not [33]), and phase (early or late [2]) of trials analyzed and the geographical location where trials were conducted [2,12]. More specifically, early development-phase studies and certain categories of disease seemed to be more prone to women's underenrollment. While a higher proportion of female have been highlighted in international trials as compared with US-only trials [12], women underenrollment also remains a topic in Europe [34,35].

Additionally, the majority of drug trials (around 80%) are sponsored by pharmaceutical companies, which are not under any mandate for inclusion of women [29,36], and their reporting of sex-specific results was shown to be lower when compared with governmentally sponsored trials (22% vs. 51% [33]).

Enrollment of women in cardiology and electrophysiology trials

While an improvement in the enrollment of women in CTs, in general, since the introduction of regulatory measures is debated, some specialties such as cardiology or oncology [30] showed particularly poor progress [8,13]. CTs from the National Heart, Lung, and Blood Institute (NHLBI) conducted between 1965 and 1998 enrolled approximately 38% of women when single-sex trials were excluded, and NHLBI trials conducted between 1997 and 2006 enrolled 27% of women [29] (Fig. 83.1). During both periods, no improvement was observed over time [8,29]. Analyses of trials from other funding sources also reported around a third of women enrolled across several CV diseases [13,37]. Within the field of cardiology, categories of diseases (such as hypertension and arrhythmia [8,11,13]) or

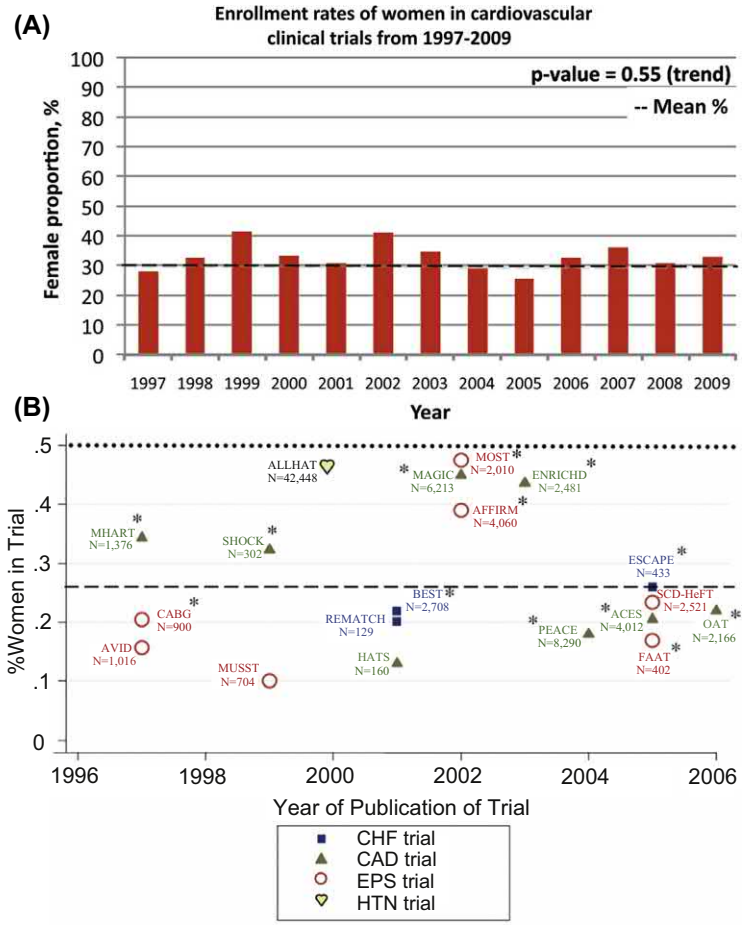

FIGURE 83.1 (A) Tsang et al. [13] analyzed the mean enrollment rates of women in 325 landmark cardiovascular (CV) clinical trials (CTs) conducted between 1997 and 2009. Over this period, no significant change in enrollment rates of women into CV trials was observed ($P = .55$). (B) Kim et al. [29] described the enrollment of women in federally funded CV randomized controlled trials (RCTs) from 1997 to 2006 by searching the NIH registry of CTs for phase 3 or 4 CV RCTs funded by the NHLBI. Each trial is represented by a marker showing the type of CV disease process it studies (*CHF*, congestive heart failure; *CAD*, coronary artery disease; *EPS*, electrophysiologic disease; *HTN*, hypertension). An asterisk by a trial name denotes that subgroup analyses based on sex were published in the primary report. The dotted line represents an arbitrarily chosen reference point of 50% enrollment, and the dashed line represents the average enrollment of women over 10 years: 27%. *NHLBI*, National Heart, Lung, and Blood Institute; *NIH*, National Institutes of Health.

trials studying devices or interventions [14,38–40] showed lower female enrollment rates than trials investigating other diseases such as CAD or conducted to assess pharmacological substances [8,41].

CV trials studying electrophysiological devices between 2000 and 2007 also reported around 28% of women [14,24], a number consistent with the percentage of women recruited in several trials assessing CV interventions [40,41], arrhythmia [13,37], implantable cardioverter defibrillator (ICD) [17], or sudden cardiac death (SCD) [36].

The problem of underreporting of sex-specific results is also preponderant in cardiology. Only 23% of CV CTs published in several journals in 2004 reported sex-specific results [33] (Fig. 83.2). This proportion was 41% for CV device trials between 2000 and 2007 ([24]) and 18% for trials of CV interventions between 1998 and 2006 [41].

Is women's underenrollment real? Consideration of population demographics

The disease prevalence for various diseases, including CV pathologies, strongly depends on sex, and recruitment rates should be adapted to these differences in prevalence instead of aiming at a 50–50 men–women inclusion rate.

As relatively young men are at higher risk for CV disease when compared with premenopausal women at the same age, it was long assumed that CV disease prevalence was markedly higher in males [1,8]. However, because of greater life expectancy in women [6], females now account for 55% of US registries for atrial fibrillation (AF), 42% for acute coronary syndrome (ACS), and 47% for heart failure (HF). Other CV conditions are still more prevalent in men, with only 23% of SCD registries population being women [36,37].

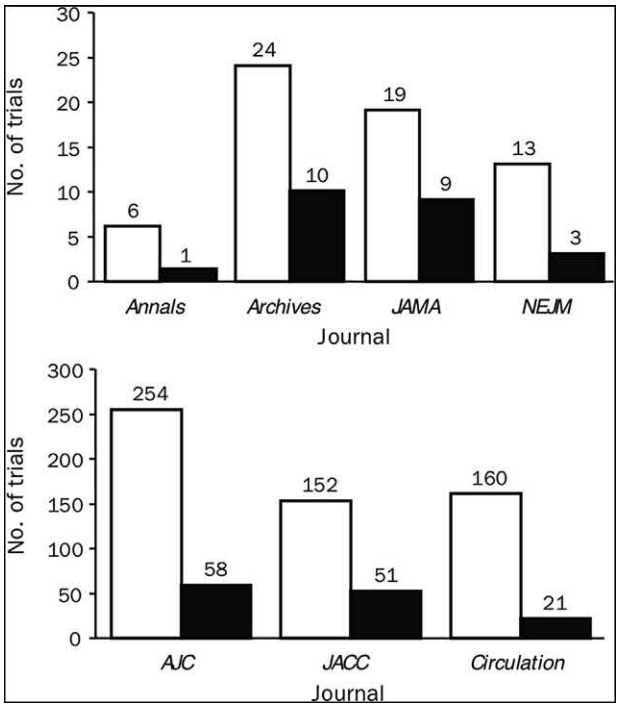

FIGURE 83.2 Blauwet et al. [33] reviewed all original adult cardiovascular clinical trials published in seven high-impact journals from July 1 through December 31, 2004. Sex-specific result reporting was defined as presenting primary outcomes for women in a format to allow the data to be abstracted for use in a metaanalysis. The figure shows sex-specific result (SSR) reporting in general medical (top) and cardiovascular (bottom) journals. *White bars* indicate the number of trials included from each journal. *Black bars* represent the number of trials in each journal that reported SSRs. A total of 23 (37%) of 62 trials reporting SSRs appeared in general medical journals and 130 (23%) of 566 appeared in cardiovascular journals. *AJC*, The American Journal of Cardiology; *Annals*, Annals of Internal Medicine; *Archives*, Archives of Internal Medicine; *JACC*, Journal of the American College of Cardiology; *JAMA*, Journal of the American Medical Association; *NEJM*, The New England Journal of Medicine.

Therefore, after accounting for age- and sex-specific differences in disease prevalence, gaps in female enrollment are more or less marked depending on the CV diseases analyzed. For instance, female enrollment in SCD trials appeared to be only 9% lower than the expected enrollment rate based on the overall population prevalence [13,29], and participation-to-prevalence ratio (PPR) of hypertensive drug trials reflected similar representation of women in the trials and in the diseased population (PPR: 0.9 [42]). On the other hand, women in ACS trials only represent 29% of the enrolled population compared with 42% prevalence in the overall population (PPR: 0.6) and 29% in HF trials against 47% in the overall population (PPR: 0.5−0.6) [37,42]. Participation and enrollment data do not seem to be homogenous for trials of AF, with some studies reporting satisfactory enrollment in pivotal AF drug trials submitted to the FDA (PPR: 0.8−1.1) while other studies highlighting an enrollment rate of only 36%−39% against 55% prevalence in the overall population [34,37,42] (Fig. 83.3A and B).

Is there a need for more women in clinical trials?

Sex-specific differences

The enrollment of a sufficient number of women is essential where differences in physiology, responses to treatments, or side effects exist due to sex. Among others, women were shown to be at higher risk of adverse response to many drugs [6,26,43], at higher risk of adverse events following ICD implantations [38,44], to experience higher death rates and serious complications after acute myocardial infarctions than men [9,11] and to undergo more target lesion revascularization following drug-eluting stent implantation [14]. These sex-based differences are explained by differences in body size [2,45], bleeding tendencies [46], and body fat content [1,10] (which affects the volume of distribution or the half-life of a variety of medications).

Importantly, as women tend to live longer and manifest CV diseases later in life, they present for CV interventions or require medications at an older age [9−13].The higher burden of comorbidities and the polypharmacy associated with increasing age put them at further risk of adverse events [47].

Impact on the health system

It seems essential to take these sex-based differences for the development of guidelines as well as for the innovation of biotechnologies and medical products [1,10,12,37,46]. An analysis based on 156 randomized controlled trials contributing to the guidelines for CV disease prevention of the American Heart Association (AHA) published in 2007 showed that enrollment of women remain relatively low when compared with their overall representation in disease populations [12]. Moreover, persistent low reporting of sex-specific analyses, with only around 25% of clinical trials conducted in the United States and in Europe providing sex-based results analysis [2], precludes the medical community to access data possibly revealing sex differences important to guidelines development [1].

Furthermore, medical research and development is quickly evolving from a blockbuster drug model to stratified medicine and ignoring such important differences might contribute to clinical trials failing in greater numbers than ever [6]. The neglection of sex differences has, for instance, led to the withdrawal of drugs from the US market, a waste of research and resources, which could have been avoided by an appropriate drug assessment in both sexes [48].

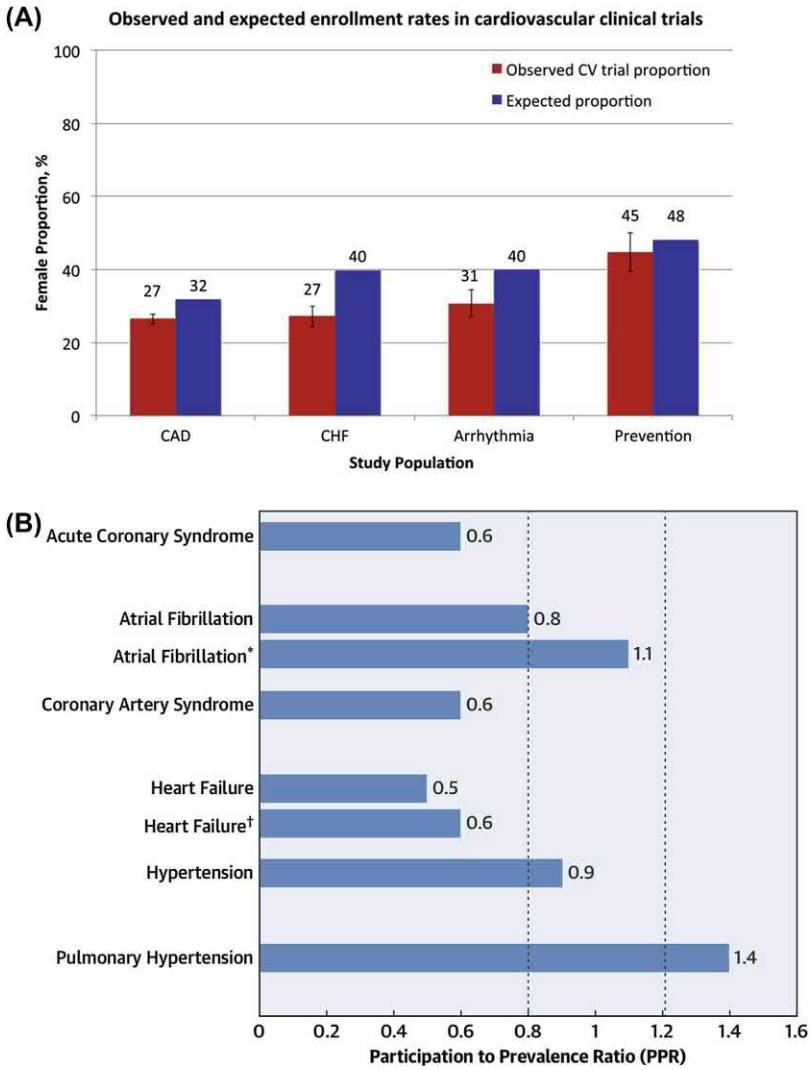

FIGURE 83.3 (A) Tsang et al. [13] compared the observed and expected enrollment rates of women in 325 landmark cardiovascular clinical trials conducted between 1997 and 2009, when accounted for sex differences in cardiovascular disease prevalence. After correcting for age- and sex-specific differences in prevalence, observed clinical trial enrollment rates of women were significantly lower than expected (5% in CAD trials, 13% in HF trials, and 9% in arrhythmia trials, all $P < .001$, when compared with expected rates). (B) Scott et al. [42] analyzed women enrollment (represented as the percentage of women among trial participants to the percentage of women among the disease population [PPR]) in trials supporting 36 cardiovascular FDA drug approvals between January 1, 2005, and September 15, 2015. A PPR of 1 indicates that the sex composition of the trial was equal to that of the disease population. A PPR between 0.8 and 1.2 (*dashed lines*) indicates that proportion of women in the trial was similar to the proportion of women in the disease population. Women were represented at a rate similar to or greater than their share of the disease population in trials in PAH (PPR 1.4), AF (PPR 0.8 to 1.1), and hypertension (PPR 0.9), with representation below a predefined range of 0.8 in HF (PPR: 0.5 to 0.6), CAD (PPR 0.6), and ACS/MI (PPR 0.6). *PPR was calculated using 2 references: one based on age-adjusted prevalence from published population-based studies and the other based on a cohort of atrial fibrillation patients within Kaiser Permanente of Northern California. †PPR was calculated using 2 references: one based on prevalence of all HF patients in the United States and the other based on the Framingham cohort with HF with reduced ejection fraction. *CAD*, coronary artery disease; *HF*, heart failure; *FDA*, Food and Drug Administration; *PAH*, pulmonary arterial hypertension; *AF*, atrial fibrillation; *ACS*, acute coronary syndrome; *MI*, myocardial infarction.

Current reasons for underrepresentation of women in cardiovascular clinical trials

Lack of education

The underrepresentation of women in clinical trials, in general, is first of all due to a lack of knowledge coming from the physicians as well as from the women themselves [6,35]. Despite a growing awareness among the female population [49], a survey conducted by the AHA in 2012 found that 44% of women were unaware that heart disease is the leading cause of death among women [6]. The lack of correct information regarding disease prevalence or sex-specific symptoms presentation and the tendency to

underestimate cardiac risk in women is also common among treating physicians [36]. Women with CAD or chronic HF (CHF) were shown to be less often referred for specialist consultation [36,50] or diagnostic testing [51].

Physicians' evaluation also determines the need for treatment and, therefore, the possibility for the patient to qualify for CTs evaluating new therapies. Physicians seem to perceive women as being at lower CV risk than men [52], and women who present with AMI are less likely than men to receive fibrinolytic drugs, stents, and related therapies [11,53–56]. This lower referral, estimated risk, and likelihood of treatment further preclude women's inclusion, especially in device-related [14,24] or interventional CTs [36].

Women's willingness to participate

The willingness of women to participate appears to be a further factor contributing to their low representation in CTs: A possible female aversion for risk-taking behaviors seems to limit the participation of female in high-risk clinical trials, such as the ones concerning devices or interventions [6–8,36].

It has been suggested that patients seek physicians of their own sex or race and that gender concordance may enhance overall patient–doctor interaction by encouraging patient's trust, improving communication and patient satisfaction [6,18]. Given the low prevalence of female physicians in certain subspecialties, such as interventional cardiology or electrophysiology, the limited identification of women to their physician was proposed as a further factor possibly reducing women's willingness to participate [19,36].

This restricted willingness seems, however, limited to specific types of CTs, as further research did not highlight any difference in refusal of enrollment in acute cardiac clinical trials by sex [57].

Study design leading to women's exclusion

Older age at the time of disease presentation or referral has also been highlighted as a factor strongly restricting women's opportunities to participate in CTs [58]. In the field of cardiology, the age dependency is especially marked for CAD, HF, or AF, all of which develop in women about 10 years later when compared with men (Fig. 83.4) [11,12,16]. As 27% of trials studying hospitalized patients with ACS in 2008–09 had an explicit age exclusion criteria as part of the study protocol, the participation of patients older than 75 or 80 years old,

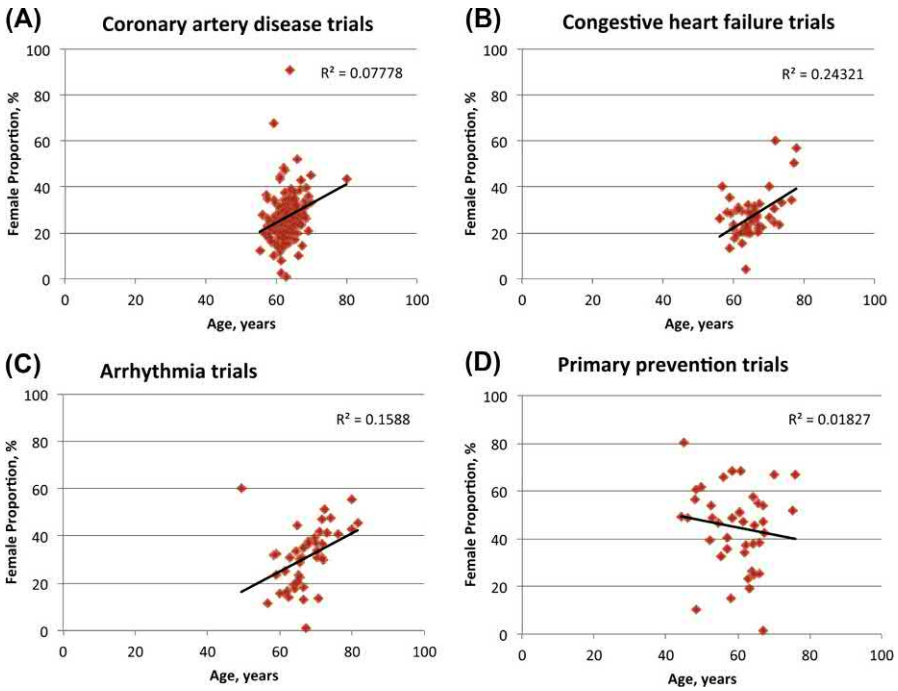

FIGURE 83.4 Tsang et al. [13] illustrated the relationship between enrollment rates of women and mean age at recruitment in trials of coronary artery disease, heart failure, arrhythmia, and primary prevention. Y-axis shows enrollment rates of women in percentages, and X-axis shows the mean age at recruitment in years. Regression line with R^2 values was reported using linear regression and Pearson's correlations. Higher women enrollment rates were observed with increasing age at recruitment in trials of (A) coronary artery disease, (B) heart failure, and (C) arrhythmia (all $P < .001$), but not for (D) primary prevention trials ($P = .40$). For every 5 years' increase in enrollment age, an increase in women's enrollment of 4.8%, 4.2%, and 4.1% in trials of coronary artery disease, heart failure, and arrhythmia, respectively, was estimated.

among which a higher proportion of women, was impossible [9]. Similarly, 21% of 325 CV landmark CTs published from 1997 to 2009 also displayed such an upper age exclusion criterion [13]. Even in the absence of age-based exclusion in study protocols, the greater prevalence of multiple comorbidities and polypharmacy with increasing age may lead to the exclusion of older women from CTs ([9]) (Table 83.1). While these exclusions are understandable from the standpoint of completing the trial safely and efficiently, the results, however, become less generalizable to people cared for outside of the context of the trial.

Other limitations criteria in CTs were shown to limit women's enrollment more acutely than men. For instance, the requirement to first reach a target dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to qualify for trials of HF medication disproportionately excluded women [59].

TABLE 83.1 Vitale et al. [58] highlighted biological, clinical, or social patients and study design or trial-related factors leading to the exclusion of elderly patients and women from cardiovascular randomized controlled trials.

	Elderly	Fertile women	Postmenopausal women
Trial-related			
Inclusion/exclusion criteria			
Chronological age	X	–	–
Potentially fertile and/or child bearing	–	X	–
Comorbidities/organ dysfunction	X	–	X
Contraindicated medication	X	–	–
Higher probability of dropout	X	–	–
More time-consuming work	X	–	–
More boring administrative work	X	–	–
Patients-related			
PK and PD factors	X	X	X
Sex hormones	–	X	X
Comorbidities/organ dysfunction	X	–	X
Polypharmacy	X	–	X
Hearing or visual defects	X	–	–
Impaired cognitive status and/or ability to provide informed consent	X	–	–
Frailty and or physical disability	X	–	–
Logistic reason			
Limited mobility/dependence	X	–	–
Family commitments	X	X	X
Family opposition	X	–	–
Physician-related			
Ageism	X	–	–
Longer time for communication/ explanation	X	–	–
Long/complex documentation	X	X	X
Longer time for informed consent	X	–	–
Need of empathy	X	X	X

PD, pharmacodynamic; *PK*, pharmacokinetic.

Structural barriers

Following years of CTs based essentially on male subjects, the recruitment and retainment experience of study leaders is more limited for women [4], and trial conduction seems to accommodate women to a lesser extent than men [6,19].

For instance, study activities were found to often be planned at time less adapted to women's than men's schedule as women are more dependent on external help to, for instance, overtake family responsibilities and childcare [19,36,60]. Moreover, other factors such as study site accessibility, availability of personal transportation, and additional costs related to the study procedures not covered by insurance were shown to limit women's participation more than men's [6,17].

Outlook for the domain of electrophysiology specifically

Scarce data are available regarding women's representation and recruitment in CT in the domain of electrophysiology specifically. However, this subspecialty displays several characteristics putting it at risk of women underenrollment. For instance, AF develops at an older age in women than men [15,16], and the mean age at recruitment has been shown to be highest in arrhythmia trials when compared with other CV trials [13]. Such a combination implies that diseased women will present with more associated comorbidities, restricted mobility, and independence, all of which might have an important impact on recruitments rate for this disease. Moreover, EP stays an interventional discipline subject to rapid technologic evolution, and the female enrollment rates in the trials assessing these new devices or procedures might be negatively impacted by the biases in referral or the lower willingness of women to take part in high-risk trials.

Strategies to increase women enrollment

Several strategies have already been introduced, whereas the implementation of other strategies still needs to further increase women's enrollment (Table 83.2).

TABLE 83.2 Pilote et al. [74] summarized the interventions to address low inclusion of women in clinical trials.

Pitfalls in drug clinical trials	Proposed interventions
Knowledge and awareness of sex and gender	
Knowledge gap in terminology, use of sex and gender as synonymous	Clarify the use of the terms *sex* and gender though educational intervention among health providers, researchers, and general population
Prescreening/screening	
Gender-related barriers for screening	Promote awareness on gender dimension
Day care Elderly Access to care	Policies to support women in day life (e.g., adequate childcare during time Spent as a research participant, assistance for elderly included in the study)
Inclusion male-pattern criteria	Inclusion criteria that consider sex differences in pathophysiology: Age Glomerular filtration rate Body size Biomarkers/diagnostic criteria
Study methodology/analysis of data	
No adjustment for relevant covariates	Prespecified subgroup analyses
Sample size leads to unpowered results	Adjusted analyses with term for sex × —drug interaction in all trials
	Adequate power for efficacy and safety analyses
Editorial policy/research output dissemination	
Lack of specific editorial requirements for sex- specific reporting in clinical trials	Journal-specific checklist for sex-specific reporting (i.e., specify the number of women in the trial, all primary and secondary endpoints by sex, discuss generalizability in both sexes)

Improving education

Patients and physicians need to be better informed and educated on several aspects of the prevalence and manifestation of CV diseases in women. As many women underestimate their risk for CV disease [61], the OWH and ORWH have already engaged in educational projects aiming at specific women's population. For instance, the WISEWOMEN program of the AHA in the United States helps uninsured or underinsured low-income women 40−64 years old to understand and reduce their risk for heart disease and stroke by providing screenings, health counseling, and community resources [62]. Similarly, the "Heart Truth" is a campaign started in 2002 and sponsored by the United States and Canada to increase awareness of the risk of heart disease in women [10,63,64]. Further programs such as the "Go Red for Women" campaign sponsored by the AHA and the "Red Dress" project sponsored by the NIH and NHLBI are public efforts to increase awareness of CV diseases as a major source of morbidity and mortality among women in the United States [49,65,66]. The scientific community also put some emphasis on improving physicians' awareness regarding women's health, as for instance, through the publication sex-specific issues in February 2017 and 2018 by the CV journal "*Circulation*," coinciding with the AHA "Go Red for Women" campaign [67,68]. Individual physicians' education as well as physician-to-patient improvement in communication is still mandated [36].

Improving trials design and recruitment strategies

Several factors leading to underrepresentation of women could be addressed during trial design and conduction. Practical barriers specific to women (such as the need for adequate childcare [19]) or due to a growingly old trial population (such as the significant handicap in vision and mobility associated with older age [47]) need to be overcome. Incorporating new technologies in recruitments strategies, such as web-based direct-to-participants tools or home study visits, could allow reduce geographical barriers, transportation costs, or scheduling difficulties [6]. Emphasizing the involvement of female clinician-researchers could lead to increased social proximity for the women enrolled.

On the other hand, statistical considerations during trial design, such as separate power calculations for men and women, would rapidly lead to impracticable costly trials of extremely large size [11,69]. Alternatively, trials could be powered to test heterogeneity in outcomes by sex: Although less rigorous than independent sex-based analysis, this approach seems far more practical as an initial step [17]. Other solutions, such as sex-stratified randomization or adaptive clinical trials could be of interest as further solutions to women's underrepresentation [11]. Moreover, the conduction and publication of sex-specific analyses, despite their likely exploratory character due to low power, would allow for the later conduction of metaanalyses and possibly merging of individual patients' data [25].

Incentives over regulations

Currently, exclusively the NIH-funded trials are subject to mandatory regulatory policies. Whether authorities should introduce further legislations also regulating non-governmentally funded trials is subject to debate, as inefficiency from increased administrative load could create more problems than it solves [1,69]. In the United States, for instance, it is within the FDA's discretion to reject an application for drug investigation or approval if the drug applicant failed to reach a satisfactory number of included women. Introducing more rigid regulations mandating a women representation in some proportion could delay therapies delivery to the market and threaten a system designed to serve the entire population [1]. Alternatively, incentivizing adequate sex representation through patent extension for studies in women could appear like an effective solution. Several 6-month extension periods of the basic 20-year patent term available to drug makers, granting them the exclusivity of the market during this time, have been delivered by the FDA for studies conducted in children. This extension had a rofound effect on pediatric research and could impact sex-specific research in a similar way [1,17].

Publishing requirements

Journals and editors seem to be in the best position to require improvement in sex-specific reporting [6]. Indeed, while advances in women's inclusion mandate efforts from the study investigators, reporting of sex-specific results requires consumers of the research results to ask for a broader dissemination of the available information [25]. A growing number of peer-reviewed journals introduced editorial policies requiring sex-specific reporting [18]. For instance, the International Committee of Medical Journal Editors advocates that researchers "aim for inclusive representative populations in all study types" for "such variables as age, sex or ethnicity" [18,70]. In addition, the European Association of Science Editors has developed a set of recommendations for reporting sex and gender in study design, data analyses, results, and interpretation of findings [18]. Scientific peer-reviewed journals themselves are also aiming at the improvement of sex-specific reporting: Already in 2005, two high-impact CV journals ("*Circulation*" [71] and "*The Journal of the American*

College of Cardiology" [72]) introduced author guidelines to provide sex-specific data in describing outcomes of epidemiological analyses and clinical trials. In 2017, a new CONSORT (Consolidated Standards of Reporting Trials) statement, the CONSORT-Equity, was released to enhance sex-specific analyses [18,73].

Conclusion

The underenrollment of women in clinical trial is not limited to but more prominent in the field of CV medicine, including EP. The disease development at an older age in women, sex-specific barriers, lack of education, and the long history of women's underenrollment in clinical trials are many factors perpetuating this tendency.

Sex differences are growingly well researched and highlighted for numerous diseases and therapies, so that the development of sex-oriented guidelines will be increasingly needed in the future. To ensure that an adequate body of evidence is available, researchers need to ensure the presence of a representative number of women in clinical trial, at least corresponding to the proportion in the diseased population (proportion-to-prevalence ratio of 1).

Teaching and increasing awareness among physicians, pharmaceutical companies, study leaders, journal editors, and the women themselves are the cornerstones to adequately include women, meaning proportionally to the number who carry the burden of the disease in the overall population.

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Chapter 84

Regulatory implications of sex differences in clinical trials

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FDA regulatory principles and implications

Introduction

This chapter will highlight some of the Food and Drug Administration (FDA) programs and initiatives to promote the study of sex differences in FDA-regulated medical devices. It will also provide a brief overview of how the FDA reviews and regulates medical device technology and will include a discussion of the regulatory implications that sex differences have in clinical trials conducted to support marketing applications. Finally, it will depict several examples to illustrate the application of these principles.

The FDA has been a pioneer of recognizing women's health needs and prioritizing regulatory research and resources to meet these needs. The FDA Office of Women's Health (OWH) was established in 1994 with the mission to advance women's health through the foundational principle that sex as a biological variable should be factored into research design, analysis, reporting, and education [1]. This office has also published a Women's Health Research Roadmap with the goal to expand research projects that inform the regulatory decision-making about the safety and effectiveness of FDA-regulated products [2]. In synergy with the OWH, the FDA's Center of Devices and Radiological Health (CDRH) also created the Health of Women (HoW) Program in 2016 to explore the issues related to the performance of medical devices in women to protect and promote the health of all women [3]. CDRH is responsible for the regulation of most cardiac devices including electrophysiology (EP) devices. This chapter focuses on the impact of sex differences on the regulation of EP devices although the regulatory implications for sex differences detected in clinical research certainly includes other devices as well. One of the priorities of the HoW Program is to encourage sex-specific analysis and reporting of medical device clinical data.

One of the FDA goals is to increase female enrollment in FDA-regulated clinical trials. In 2008, the FDA organized a workshop to discuss ways to overcome barriers to understanding the impact of sex on clinical outcomes. The participants, which represented government agencies, medical societies, and patient advocacy groups, suggested the following reasons for lower female enrollment in clinical trials [4]:

1. Lack of understanding about main obstacles to participation of women in clinical research.
2. Fear of fetal consequences if a female participant becomes pregnant (e.g., effects of radiographic assessments or concomitant drug therapy).
3. Inclusion/exclusion criteria potentially not needed to define the study population may unintentionally exclude women (e.g., upper age limit).
4. Lack of understanding about differences in disease etiology and pathophysiology may lead to underdiagnosis and underreferral of women.
5. Investigator and sponsor avoidance of female patients due to the perception that it takes more time and money to recruit them.
6. Family responsibilities limiting women's ability to commit time for study follow-up; in the consensus document on sex differences in cardiac arrhythmia, the European Heart Rhythm Association also states that females are referred later than males for invasive

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procedures, which could also be a contributor to lower female enrollment in clinical trials of electrophysiology devices [5]. To understand the scope of female enrollment, the following section will describe the current landscape of clinical trials for electrophysiology devices. This section will also include a discussion of the principles and initiatives been undertaken to promote female enrollment and reporting of sex-specific outcomes in FDA-regulated trials.

Sex differences in FDA-approved electrophysiology devices

To understand the impact of sex differences in EP devices trials, the authors analyzed the data taken from the Summary of Safety and Effectiveness Data (SSED) of the EP devices approved between 2009 and 2018 after the FDA's review of their original premarket approval (PMA) application, excluding automated external defibrillators. An SSED includes a summary of the design and results of the relevant clinical trial(s) and is made available to the public when the FDA approves the PMA application, which is necessary to market-release the device. Out of the 16 SSEDs analyzed, 15 involved studies that reported enrollment by sex in their clinical trials. The proportion of female subjects enrolled in these trials ranged from 14.9% to 45% with an average enrollment of only 33.9%, and this trend is reflected in Fig. 84.1. Although the level of female enrollment was similar to those reported in the electrophysiology literature [5,6], low female enrollment presents a regulatory challenge when assessing the clinical and regulatory impact of observed differences that are not statistically significant likely due to the small sample size of the female cohort.

Of the 16 original SSEDs reviewed, only eight provided a subgroup analysis exploring differences in outcomes by sex. Although sex differences were observed in several device studies (discussed later in this chapter), these studies were not statistically powered to detect outcome differences between the sexes. When sex differences were observed in these clinical trials, they were described in a section of the SSED along with a discussion on the possible physiologic, anatomic, or societal factors that may have contributed to the sex differences seen. Although differences were observed in the eight studies with a sex-based subgroup analysis, they did not raise clinical concerns to the level that would otherwise preclude a device approval or result in different labeling and indications based on sex.

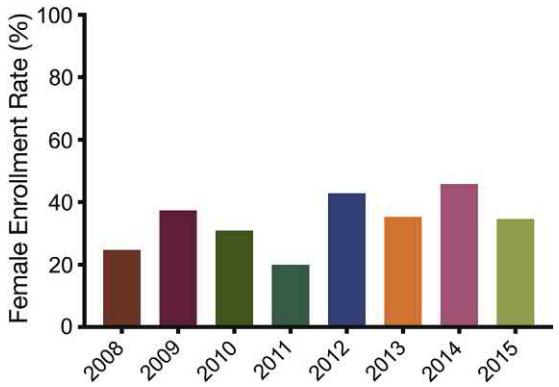

FIGURE 84.1 Female enrollment trend. Each bar in the plot represents the average female enrollment rate of the PMA applications submitted in a given year. *PMA*, premarket approval.

The FDA has made tremendous efforts to raise awareness among many stakeholders about the underrepresentation of females in medical device clinical trials. This has led many sponsors to improve their recruiting techniques to promote female enrollment and to publicly provide the descriptive results of the subgroup analysis by sex. However, the fact that only half of the SSEDs analyzed here reported sex-specific outcomes highlights the need for CDRH's current strategies to promote consistent sex-specific data collection, analysis, and reporting and underscores the importance of the Health of Women Program to overcome these obstacles [7].

Regulatory processes and principles

To regulate devices efficiently, the FDA classifies devices in three different risk-based categories with class III encompassing the category of devices with the highest level of risk. Although there are many diagnostic electrophysiology devices that belong to class II category, the majority of devices intended for treatment of cardiac arrhythmias are class III devices; therefore, we will focus on their regulatory process in this discussion.

Investigational device exemption process: Center of Devices and Radiological Health clinical trials

For class III devices to enter the US market, a PMA application needs to be submitted to the FDA demonstrating safety and effectiveness of the device for the proposed intended use. However, most PMA application devices need clinical data for this determination to be made. To conduct a clinical study on a significant risk investigational device in the United States, an investigational device exemption (IDE) needs to be approved by the FDA to collect the clinical data required to support the PMA application. During the IDE review, the FDA ensures that sufficient safety protections are in place, and the agency may provide recommendations to strengthen the study design.

In 2014, CDRH published a guidance document titled "Evaluation of Sex-Specific Data in Medical Device

Clinical Studies" [4]. One of the goals of this guidance was to improve the quality and consistency of available data regarding the performance of medical devices in both sexes by encouraging appropriate enrollment by sex in clinical studies of devices. This guidance suggests that when planning the study, the following aspects should be considered to identify potential sex differences:

1. sex-specific prevalence;
2. sex-specific diagnosis and treatment patterns;
3. identification of proportions of women included in past studies for the target indication;
4. identification of any known clinically meaningful sex differences in outcomes related to either safety or effectiveness.

Sponsors should make every effort to identify in advance any key covariates that might explain possible differences across sexes, to plan to collect data on these covariates, and to prespecify an approach to investigate the extent to which these covariates can explain the observed differences. This information should be included in the risk analysis of the investigational plan and should be summarized in the study protocol and investigator training to highlight the importance of enrolling representative proportions of women and men that are consistent with the disease prevalence [4].

Premarket approval application review: data analysis and interpretation

Once the clinical trial is completed, a PMA application is submitted to the agency to request marketing approval of the device. The review of a PMA application is a four-step review process, which includes an in-depth scientific, regulatory, and quality system review by appropriate FDA personnel [8]. As explained in the 2014 "Evaluation of Sex-Specific Data in Medical Device Clinical Studies" guidance, descriptive statistics for outcomes of interest by sex should be provided, as well as the influence of sex on primary endpoints for both safety and effectiveness [4]. If any clinically meaningful sex differences are found, either based on prespecified or exploratory post hoc analyses, the sponsor should discuss with the FDA whether additional data are needed to address any remaining sex-specific questions.

When the safety and effectiveness of the device has been determined and the PMA application is ready to be approved, the guidance also recommends that public documents, including the SSED and labeling, report the number and proportion of subjects by sex who were treated or diagnosed with the device as part of the clinical study. Information regarding sex-specific outcomes analyses should be provided, and any covariates that might explain possible outcome differences between sexes should be described. In cases where clinically meaningful sex differences are found, data on benefits and risks should be described separately for women and men in the device labeling and SSEDs. If results of the analysis suggest that there is insufficient data to assess whether sex is associated with clinically meaningful differences in outcome, the FDA may determine that clinical data from additional subjects in one or both sexes may be needed [4].

Postapproval study design and analysis

To help assure the continued safety and effectiveness of an approved device, the agency may require a postapproval study (PAS) as a condition of approval under 21 CFR 814.82(a) [2]. A PAS may be a clinical or nonclinical study and is intended to gather specific information to address questions about the postmarket performance of an approved medical device. If a subgroup of subjects (e.g., younger subjects or a particular sex) was underrepresented in the premarket study, the FDA may request that more of these subjects be enrolled in the PAS to gather additional information on the whole target patient population [9].

The FDA recommends that the PAS protocol be agreed upon between the agency and the sponsor before the time of PMA application. The key study elements normally include study objectives, study design, sample size, safety and/or effectiveness endpoints, and follow-up frequency and length. The statistical analysis plan may be submitted together with other elements for a full protocol review.

The study design commonly includes randomized clinical trial, prospective and retrospective cohort study, cross-sectional study, case–control study, and a few relatively newer study designs such as enhanced or active surveillance, metaanalysis, and comprehensive-linked/registry-based surveillance.

Labeling update

If a clinically or statistically meaningful sex difference is detected in the PAS (i.e., more data collected during real-world commercialization phase), the FDA may recommend the sponsor to update the originally approved labeling (e.g., warning or caution sections) and SSED so that the public, particularly patients and providers, will be timely informed of updated differences, which might include updated sex information.

Regulatory examples

Catheter ablation devices for the treatment of atrial fibrillation

Atrial fibrillation (AF) is an important public health problem. It affects 33 million patients worldwide including 3–5

million Americans and is associated with an increased risk of stroke and mortality [10–14]. The prevalence of AF is lower at all ages in women than in men. However, since women with AF are older, the absolute number of men and women with AF is about equal [15]. In the past two decades, catheter ablation has evolved from an experimental therapy to an important therapeutic option for rhythm control in patients with AF, especially those with symptomatic paroxysmal or persistent AF who have failed antiarrhythmic drug (AAD) therapy. Although women are more symptomatic from AF and are less tolerant to AADs than men, the referral rate of women for AF ablation has been significantly lower than men, which contributed at least in part to the smaller proportion of women enrolled in observations studies and randomized control trials of AF ablation [16–20]. While most of the AF ablation studies reported greater complication rates in women, there are less consistent data on the impact of sex on ablation success. After a review of the relevant literature, the writing group of the 2017 Heart Rhythm Society (HRS) Expert Consensus Statement on Catheter and Surgical Ablation of AF concluded that overall studies have not shown a significant sex-related difference in outcomes with AF ablation, whereas the 2018 European Heart Rhythm Association (EHRA) Consensus Document on Sex Differences in Cardiac Arrhythmia concluded that women seem to respond less favorably to AF ablation [5,21].

In the United States, ablation catheters indicated for the treatment of AF are currently classified as class III devices, and their market approval requires clinical data to demonstrate a reasonable assurance of safety and effectiveness. As of January 2019, a total of five pivotal studies have been successfully conducted and supported the FDA approval of a new ablation catheter for an AF indication or a previously approved catheter to include an AF indication [22–26]. Among them, all three studies completed after and one before the publication of the FDA Guidance on Evaluation of Sex-Specific Data in Medical Device Clinical Studies reported the results of sex analysis in the SSED published by the FDA. As shown in Table 84.1 and Fig. 84.2, the proportion of women enrolled in the four [4] studies with sex analysis in the SSED ranged from 31% to 38%. The representation of women in these studies was considered adequate since the proportion of women enrolled was in line with that reported in other AF ablation trials and registries [18–20,27]. Of note, none of the studies was powered to test the study hypotheses separately in men and women. Rather, the impact of sex on primary endpoints was assessed as an exploratory analysis. Summary tables by sex and treatment groups were presented in three SSEDs, whereas a multivariate analysis was performed to assess the association between sex and study outcomes in three studies.

Consistent with the conclusion in the 2017 HRS Expert Consensus Statement on Catheter and Surgical Ablation of AF [21], 1-year success did not differ significantly between men and women in any of studies in which sex analysis was performed as depicted in Figs. 84.3 and 84.4.

On the safety side, a signal of sex disparity was identified in one pivotal study only. In the HeartLight study [25], the primary safety event rate was higher in female subjects following laser balloon ablation compared with female controls and male subjects treated with the study device. This difference was primarily driven by a high incidence of phrenic nerve injury in female subjects treated with the HeartLight laser balloon ablation system. Treatment-by-sex interaction assessed by logistical regression analysis reached statistical significance, suggesting that males and females may have different safety profiles for the HeartLight system as compared with the control catheter. However, since the number of female subjects enrolled in the study was small (52 females in the study group), no firm conclusion could be made regarding the safety profile of the laser balloon in women. Moreover, there was no known anatomical or clinical reason for sex disparity in the risk of phrenic nerve injury associated with laser balloon ablation. The study device was eventually approved by the FDA for the treatment of symptomatic drug refractory paroxysmal AF without sex restriction base on the totality of safety and effectiveness data. Because of the safety signal identified in the pivotal study, a PAS was ordered as a condition of approval and required enrollment of a large number of female subjects to further inform the safety profile of the study device including the risk of phrenic injury in women. Fig. 84.5 depicts the overall primary safety event rate in these studies.

Cardiovascular implantable electronic devices

Cardiovascular implantable electronic devices (CIEDs) encompass pacemakers, implantable cardioverter defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices. These are class III devices that are market-approved via the PMA pathway [28]. They provide lifesaving therapy for patients with bradyarrhythmias, tachyarrhythmias such as ventricular tachycardia, and heart failure in the case of CRT. These benefits are seen in both men and women; however, differences have been observed with respect to the rates of adverse events and even benefit in the case of CRT. Many of the FDA's recent initiatives to assess device safety and effectiveness with respect to sex and to try to increase female enrollment were developed after some of the earlier pacemaker and ICD studies showed that there may be a sex difference.

The use of pacemakers has steadily increased since the first one was implanted in the 1960s, and now, millions of patients worldwide are living with a pacemaker [29].

TABLE 84.1 Sex-specific outcomes in catheter atrial fibrillation (AF) ablation device approval studies.

Trial Name/Device name	Year of device approval	Trial Design	AF type	Women in study device arm n/N (%)	Sex analysis performed	One-year success		Primary safety event rate	
						F	M	F	M
ThermoCool AF (22)/NaviStar ThermoCool	2009	RCT	PAF	33/106 (31)	Yes	66%[a]		10.8[a]	
STOP AF (23)/Arctic Front Cryoballoon	2010	RCT	PAF	38/163 (23)	No	70%[b]		3.1%[b]	
TOCCASTART (24)/TactiCath	2014	RCT	PAF	52/152 (34)	Yes	67%	68%	2%[c]	
HeartLight (25) /HL balloon	2016	RCT	PAF	52/170 (31)	Yes	59%	62%	25%	5.9%
ZERO-AF (26) /Blazer OR	2017	RCT	PAF	62/167 (37)	Yes	53%	72%	12%	10%

PAF, paroxysmal AF; *F*, female; *M*, male; *RCT*, randomized controlled trial.
[a]*Sex-specific chronic success at one year and primary adverse event rate were not reported. Multivariate logistic regression was performed and showed that gender was not a significant predictor of the primary effectiveness or safety outcomes.*
[b]*Sex analysis was not performed for the primary effectiveness or safety endpoints.*
[c]*Sex-specific primary safety event rate was not reported and only three subjects experienced primary safety events in the study device group.*

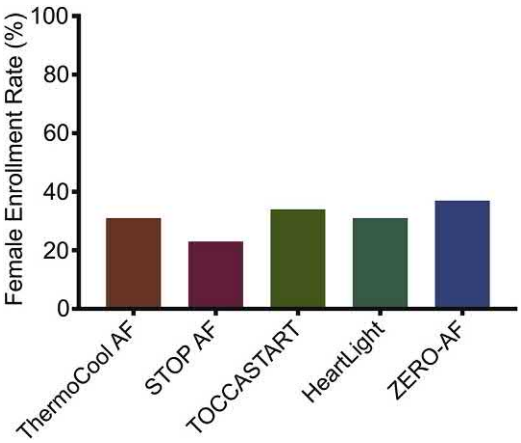

FIGURE 84.2 Female enrollment in device arm.

In the early 2000s, there was significant debate over the benefit of single-chamber ventricular versus dual-chamber pacemaker therapy. One study, the Mode Selection in Sinus Node Dysfunction (MOST) study, which implanted dual-chamber pacemakers and randomized over 2000 patients to ventricular-only or atrial and ventricular dual-chamber synchronous pacing, looked at procedure- and device-related complication rates. The univariate analysis as well as the multivariate model both showed female sex to be the only predictor that showed a trend toward an association of a higher complication rate with a hazard ratio (HR) of 1.40 in the multivariate analysis (95% confidence interval: 0.98−1.99, $P = .06$). Interestingly, the increased complication rate did not appear to be related to age, weight, history of heart failure or prior myocardial infarction, or body mass index. The 30-day complication rate for women also showed an increased trend with a rate of 6.0% compared with 3.8% for men ($P = .07$) [30]. Another prospective pacemaker study, the FOLLOWPACE study, which was conducted in the Netherlands, assessed pacemaker complications in 1517 patients where 56.4% were men. When looking at procedural and early complications (within 2 months of implant), a multivariable analysis similarly showed that men had a significant lower risk of complications with an HR of 0.72 (95% confidence interval: 0.53−0.97, $P = .03$) compared with women [31].

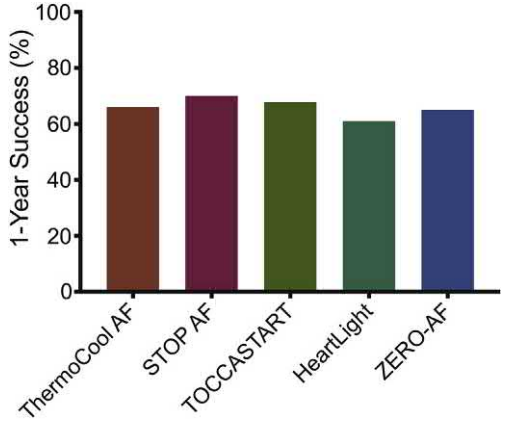

FIGURE 84.3 Overall 1-year ablation success.

More recently, with the introduction of the single-chamber leadless pacemaker, such as the Medtronic Micra Model MC1VR01, premarket clinical studies were conducted to assess its safety and effectiveness since it is markedly different from transvenous pacemakers. In the Micra TPS study, which was conducted under IDE, women comprised 41% of implanted patients [32]. Sex was one of the prospectively identified subgroups of interest, and the investigators found that although both men and women had an acceptable 6-month complication free rate that was above the prespecified performance goal of 83%, women did have significantly more complications (complication-free rate of 93.8% for women and 97.5% for men with a P value of 0.0185). This appeared to be due to more instances of cardiac perforation and pericardial effusion, which occurred 2.68% and 0.7% of the time, respectively. Women in the study were more likely to weigh less and have heart failure, whereas the men were more likely to have coronary artery disease; it is unclear if these differences contributed to the different complication rates or not.

The more recent pacing lead clinical studies can also sometimes have prespecified sex analyses requested by the FDA. One example is the premarket clinical trial for the Medtronic Attain Ability Model 4196 Lead. This is a pacing lead, which is placed in a cardiac vein via the coronary sinus to pace the left ventricle and be used with a CRT system. Of the 146 enrollees, only 36 (24.7%) were women. Although women seemed to have a higher pacing capture threshold, there was no discernible difference with respect to safety and adverse events [33].

ICDs, similar to pacemakers, have shown effectiveness in treating arrhythmias in both men and women. However, they do seem to confer a greater complication rate. Haines et al. created a Risk Score Model to help identify which patients undergoing ICD implant were at greater risk for acute procedural complications [34]. They analyzed over 260,000 ICD implants submitted to the National Cardiovascular Data Registry (NCDR) for ICDs between 2006 and 2008 to create the risk model, which consists of 10 variables including female sex. Women comprised 25.9% of the total population and had a complication rate of 3.9% compared with the overall complication rate of 3.2%. Another study using the NCDR ICD Registry, specifically looking at cardiac perforation during initial ICD and CRT defibrillator implants, examined the records of over 440,000 enrollees between 2006 and 2011 and found that the overall perforation rate was 0.14% [35]. After a multivariable adjustment, they determined that there were six factors associated with greater odds of perforation

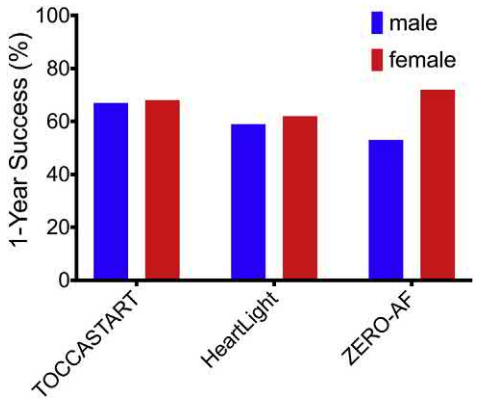

FIGURE 84.4 Sex-specific 1-year success.

including female sex. The adjusted odds ratio for women was 2.18 (95% confidence interval: 1.86−2.57, $P < .0001$). The authors hypothesized that this may be due to women having a thinner and smaller right ventricular myocardium. Fortunately, ICD studies, such as the landmark MADIT II trial looking at primary prevention defibrillator therapy, have not shown a difference in survival benefit between men and women [36]. The subcutaneous implantable defibrillator (S-ICD) clinical trial was also analyzed for various subgroup differences including a sex analysis, which showed that women had a greater risk of discomfort from the device but not an increased risk of inappropriate shocks or other complications such as infection [37].

Resynchronization therapy, delivered by biventricular pacemakers and ICDs, is a relatively newer technology and has also been studied to assess whether an interaction between patient sex and treatment with CRT exists. The COMPANION study that was looking at the effectiveness of biventricular pacing in NYHA class III/IV patients with an ejection fraction of $\leq$35% and a QRS duration $\geq$120 ms did not find any difference in effectiveness in terms of heart failure hospitalization and all-cause mortality between men and women [38,39]. Approximately, 32% of the total cohort was female. Subsequently, the MADIT-CRT study, with a female enrollment of 25%, was conducted to assess the effectiveness of CRT in NYHA class I/II patients. Sex was again a prespecified analysis, and the results were unique in the realm of cardiac devices; an interaction between sex and CRT treatment was found where women derived greater benefit than men. This was hypothesized by the FDA to be due to a greater prevalence of left bundle branch block (LBBB) in the female enrollees and ultimately led to a post hoc analysis of LBBB subjects. However, even when looking at only subjects with LBBB, women still appeared to benefit more than men with a greater survival free of a heart failure event [40]. This led the MADIT-CRT investigators to further analyze the results in terms of effectiveness of CRT in men and women [39], and the FDA also performed a follow-up metaanalysis looking at the benefit of CRT in women as a function of LBBB and QRS duration [41]. The metaanalysis demonstrated that women with LBBB benefitted from CRT at a narrower QRS duration than men with LBBB, suggesting that a given QRS duration may indicate more dyssynchrony in female patients compared with male patients with the same QRS width.

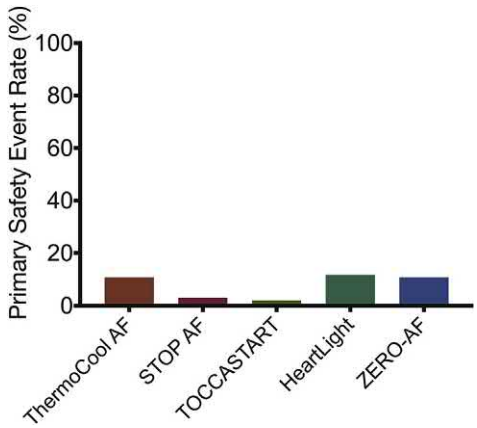

FIGURE 84.5 Overall primary safety event rate.

Conclusion

The FDA has recognized that there can be sex differences with respect to various medical treatments in general, and the FDA's CDRH has specifically sought to assess these sex differences for medical devices. This awareness has led to efforts to increase female enrollment into clinical trials and to look at sex as one of the key subgroup analyses.

The more recent regulated clinical trials analyzed within EP have demonstrated that there are differences among the sexes; women, in general, tended to have higher complication event rates although often with similar effectiveness results. To pursue these analyses, adequate representation of each sex was needed. From a regulatory perspective, it is important to report these differences even if they might not limit the approval of the device to only one sex or have different labeling or indications based on sex. There clearly are differences between men and women when looking at device and ablation adverse event rates, and investigating these may lead to a better understanding of the underlying risks for adverse events or reduced response to the therapy. For example, when looking at CRT effectiveness, the greater benefit in women was a surprise, which led to further analyses and a better understanding of the underlying pathophysiology in heart failure patients with a wide QRS. As new ablation and device technologies are developed and tested, the FDA will continue to examine the sex differences in terms of both safety and effectiveness. Moreover, the agency will continue to ensure that data in

both sexes are reported publicly (e.g., SSED and labeling) to help healthcare providers and their patients better understand the individual benefit/risk ratio to make informed clinical decisions.

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Index

Note: Page numbers followed by "*f*" indicate figures and "*t*" indicate tables and "*b*" indicate boxes.

B

C

D

E

F

G

H

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z

Sex and Cardiac Electrophysiology

Edited by Marek Malik

Sex and Cardiac Electrophysiology: Differences in Cardiac Electrical Disorders Between Women and Men is a comprehensive investigation into all aspects of sex differences in cardiac electrophysiology. It is now well recognized that in many medical fields, there are substantial differences between female and male patients in physiology, pathology triggering factors, disease progression, clinical approaches, and treatment outcome. In cardiology, the differences between women and men are more recognized in comparison to many of these other medical fields. At the same time, recent advances in the understanding of cardiac arrhythmias, sudden arrhythmic death, and cardiac electrophysiology, in general, show that there are substantial but frequently ignored sex differences also in this field. This title will summarize these important differences to provide the essential information needed for clinical specialists and researchers involved in the design and conduct of clinical studies on the differences between sexes and on the physiologic background and clinical implications of these differences.

Key Features

- Explores topics ranging from the physiologic differences between women and men to the differences in clinical handling of arrhythmic disorders between female and male patients.
- Covers individual aspects of sex differences in cardiac electrophysiology in separate chapters by international specialists.
- Covers the sex differences of cardiac electrical disorders providing insight beyond cardiac metabolic syndrome, hypertension, atherogenesis, and heart failure.

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