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Sex-Related Differences in Cardiac Channelopathies

Implications for Clinical Practice

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ABSTRACT: Sex-related differences in prevalence, clinical presentation, and outcome of cardiac channelopathies are increasingly recognized, despite their autosomal transmission and hence equal genetic predisposition among sexes. In congenital long-QT syndrome, adult women carry a greater risk for Torsades de pointes and sudden cardiac death than do men. In contrast, Brugada syndrome is observed predominantly in adult men, with a considerably higher risk of arrhythmic sudden cardiac death in adult men than in women. In both conditions, the risk for arrhythmias varies with age. Sex-associated differences appear less evident in other cardiac channelopathies, likely a reflection of their rare(r) occurrence and our limited knowledge. In several cardiac channelopathies, sex-specific predictors of outcome have been identified. Together with genetic and environmental factors, sex hormones contribute to the sex-related disparities in cardiac channelopathies through modulation of the expression and function of cardiac ion channels. Despite these insights, essential knowledge gaps exist in the mechanistic understanding of these differences, warranting further investigation. Precise application of the available knowledge may improve the individualized care of patients with cardiac channelopathies. Promoting the reporting of sex-related phenotype and outcome parameters in clinical and experimental studies and advancing research on cardiac channelopathy animal models should translate into improved patient outcomes. This review provides a critical digest of the current evidence for sex-related differences in cardiac channelopathies and emphasizes their clinical implications and remaining gaps requiring further research.

Key Words: arrhythmias, cardiac ■ Brugada syndrome ■ death, sudden, cardiac ■ gender identity ■ genetics ■ long QT syndrome ■ sex

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Cardiac channelopathies are heritable disorders caused by pathogenic variants in genes encoding cardiac ion channel subunits and ancillary proteins that maintain the electromechanical function of human cardiomyocytes.[1] Collectively, cardiac channelopathies

are estimated to underlie up to 10% of all sudden cardiac deaths (SCDs),[2] most of which occur in individuals <40 years of age.[3,4] Cardiac channelopathies are typically inherited in an autosomal dominant manner, meaning that first-degree family members have a 50% chance of inheriting the variant that predisposes to disease.[1] Most cardiac channelopathies show incomplete penetrance and variable expressivity whereby family members who carry the same variant sometimes have a wide range of different phenotypes.[5,6]

A wide array of genetic, posttranslational, and environmental factors that influence the cardiac channelopathy phenotype are being recognized (Figure 1).[6] Emerging evidence suggests that biological sex, resulting in part from genetic and environmental factors and in part through the multifaceted effects of sex hormones on cardiac ion channels, is important in determining clinical course in cardiac channelopathies.[7–10] Furthermore, men and women with certain cardiac channelopathies show differences in age-related penetrance, disease expression, and risk for SCD.[11] Nonetheless, there is limited awareness of sex-related differences in clinical manifestations of cardiac channelopathies and risks in different reproductive phases in life. Findings from large cohort studies are often extrapolated to both sexes without consideration of relevant sex-related variances.

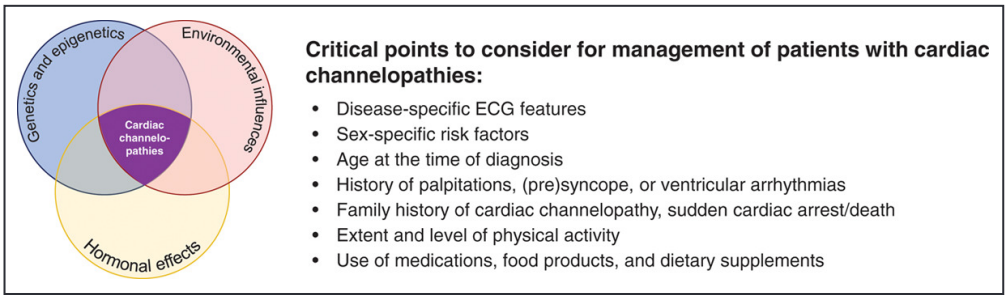

Figure 1. Critical points to consider for management of patients with cardiac channelopathies.

In this review, we summarize the compelling evidence for sex-related differences and their underlying mechanisms in cardiac channelopathies, their clinical implications for patient management, and how future research relevant to the elucidation of sex as a modifier of phenotype can improve the precision of care of cardiac channelopathy patients.

SEX DIFFERENCES IN NORMAL CARDIAC ELECTROPHYSIOLOGY PARAMETERS

Significant sex-related differences in electrocardiographic features have been recognized for decades. Men have longer PR intervals and P-wave and QRS durations than do women, whereas resting heart rate is higher and heart rate corrected QT intervals (QTc) are longer in adult women.[12] Although QTc is similar in boys and girls at birth and during childhood, sex-related differences become evident with the onset of puberty as a result of QT shortening in male and QT prolongation in female patients and diminish after menopause, indicating an effect of sex hormones, particularly testosterone, on cardiac repolarization.[12–14] In addition, at puberty, boys develop a typical pattern of ventricular repolarization, characterized by a higher amplitude of the J point, a shorter and steeper ST-segment course, a steeper ascent, and a higher amplitude of the T wave.[15] The QT interval is also affected by the menstrual cycle, with shorter durations observed in the luteal than in the follicular phase, attributed mainly to the increased progesterone levels during

the luteal phase.[16] In addition, the QT/RR slope is steeper in women than in men, such that sex differences in QTc are more pronounced at slow heart rates.[17]

Sex-specific variations in normal cardiac electrophysiology and susceptibility to arrhythmias have been ascribed mainly to genetic factors and hormonal influences. Differences in autonomic tone, hemodynamics, nonsteroid hormone levels, and homeostatic response to defective ion channels (eg, changes in expression of other ion channels) may also contribute to sex-related disparities, but these mechanisms are not yet fully understood.

LONG-QT SYNDROME

Congenital long-QT syndrome (LQTS) is a primary disorder of cardiac repolarization characterized by a prolonged QT interval on the surface ECG and predisposition to arrhythmic syncope, Torsades de pointes (TdP), and SCD at a young age.[18] Although 17 genes have been implicated in LQTS, in a recent evidence-based assessment, only 3 genes—*KCNQ1, KCNH2* and *SCN5A*—were found to have definitive evidence for causing typical LQTS.[19] Variants in these 3 genes collectively explain ≈90% of all genotype-positive cases.[20] *KCNQ1* (LQTS type 1 [LQT1]) and *KCNH2* (LQTS type 2 [LQT2]) encode the α subunits of voltage-gated repolarizing K^+ channels conducting I_{Ks} and I_{Kr}, respectively, whereas *SCN5A* (LQTS type 3 [LQT3]) encodes the α subunit $Na_V1.5$ of the cardiac Na^+ channel, conducting I_{Na} and, in case of variants, pathological late $I_{Na,L}$.[18]

Sex-Related Differences in Clinical Phenotype

Significant sex-related differences in the QT interval, as well as implications for sex-based risk assessment and management, are well recognized in LQTS. Because of the longer QT intervals in healthy women, sex-specific cutoffs for defining a prolonged QT interval were determined: 470 milliseconds in men and 480 milliseconds in women (Figure 2).[21] Among LQTS variant carriers, the clinical penetrance of disease is higher in women than in men.[7] In the largest multicenter registry reported so far, women comprised 56% of all patients with LQTS (Figure 3).[22,23] As in the general population, women with LQTS (particularly LQT1 and LQT2) have longer QTc intervals than their male counterparts.[29] Women are more prone to QT prolongation at slower heart rates; therefore, evaluation of QTc at rest, particularly at night, is important for risk stratification.[29] Furthermore, adult women with LQTS are generally at increased risk of TdP compared with male individuals and prepubescent girls.[30]

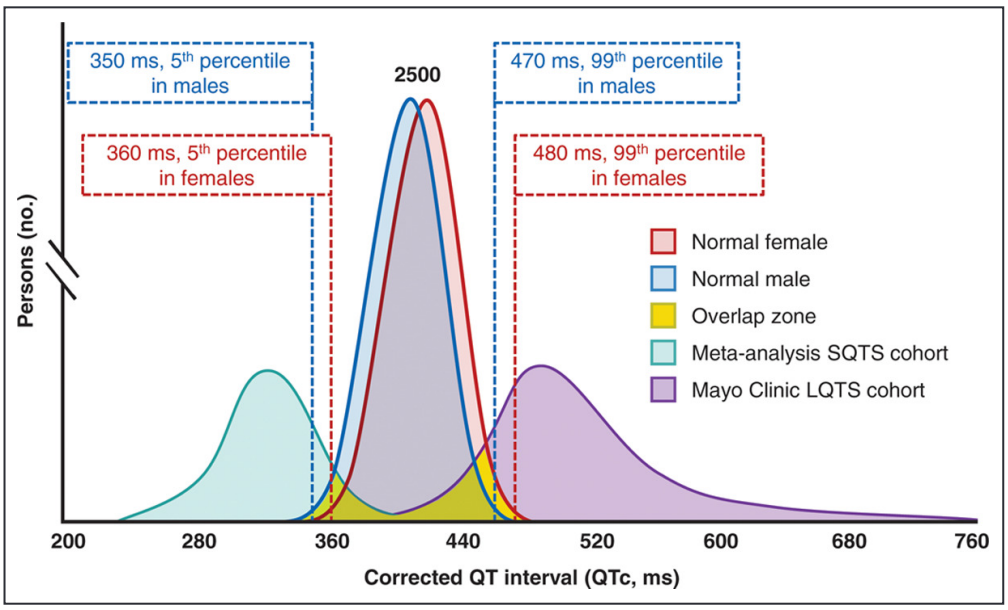

Figure 2. Heart rate–corrected QT interval distribution in health and disease. LQTS indicates long-QT syndrome; and SQTS, short-QT syndrome. Modified from Giudicessi and Ackerman[6] with permission. Copyright © 2013, Elsevier.

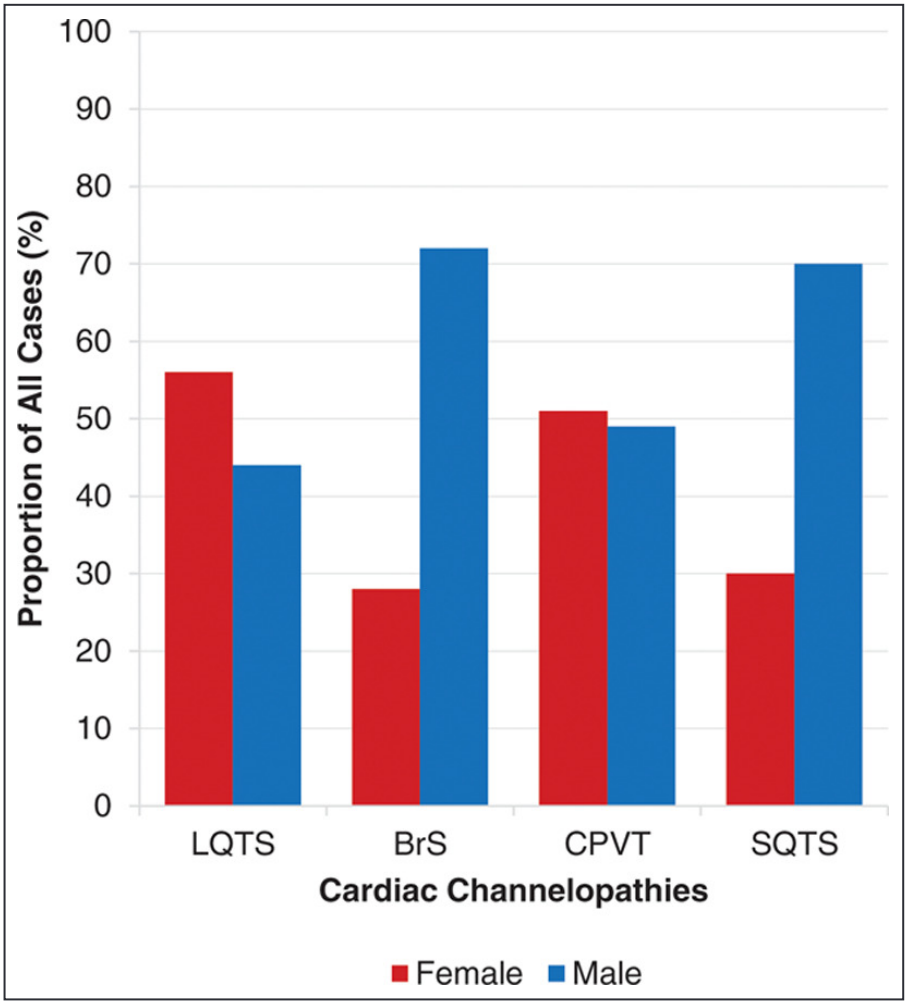

Figure 3. Approximate sex distribution of patients diagnosed with cardiac channelopathies. For long-QT syndrome (LQTS), proportions are based on the report of Kutyifa et al,[23] which included only genetically confirmed LQTS cases from the Rochester-based LQTS registry. For Brugada syndrome (BrS), proportions represent the average of reports by Sieira et al,[24] Milman et al,[25] and Berthome et al.[26] The diagnosis of BrS in these studies was made according to the criteria defined in the international guidelines.[1] For catecholaminergic polymorphic ventricular tachycardia (CPVT), proportions are based on the report by Roston et al.[27] The diagnosis of CPVT in this study was made according to the criteria defined in the international guidelines.[1] For short-QT syndrome (SQTS), proportions are based on the meta-analysis of all SQTS cases by El-Battrawy et al.[28]

In general, male patients with LQTS have a greater risk of fatal presentation of the disease, whereas female patients typically experience recurrent, nonfatal events such as syncopal episodes, likely related to self-terminating TdPs.[7] In childhood and before puberty, boys with LQT1 have an increased risk for arrhythmias compared with girls, but the risk of arrhythmias is similar in male and female individuals with LQT2 or LQT3.[11] However, after puberty, the risk of experiencing arrhythmias in patients with LQT1 reverses, with female patients being at higher risk.[7] Postpubertal female patients with LQT2 have a higher risk for ventricular arrhythmias compared with men,[11] and the risk stays elevated after menopause,[31] implying that there is a need for life-long therapy in these patients.

Studies have found that men with LQT1 and LQT2 present earlier in life with a cardiac phenotype than do their female counterparts.[32] Both female patients with LQT2 and male patients with LQT3 are at elevated risk of experiencing an arrhythmic event before 40 years of age than their male counterparts with LQT2 and female counterparts with LQT3, respectively.[32] In LQT3, women are at higher risk for SCD, particularly in the age group of 30 to 40 years.[33]

Female sex has also been shown to increase the risk of TdP associated with cardiovascular[34] and noncardiovascular drugs.[35] Furthermore, a study investigating a large cohort of patients with acquired atrioventricular block found relevant sex differences in the association of QT interval duration with the risk of TdP at bradycardia.[36] Although longer QTc intervals were associated with a higher risk of TdP in both sexes, women were susceptible to TdP at shorter QTc durations that were not necessarily arrhythmogenic for men, indicating that female sex is an independent predictor of TdP.[36]

Hormonal Influences Underlying Sex-Related Differences

Although the exact mechanisms for all sex-related disparities remain uncertain, sex hormones are known to modulate the phenotype in LQTS (Figure 4).[13] In animal models, estrogen increased the duration of the QT interval through mechanisms similar to its physiological effect on ionic currents (Table), whereas endogenous progesterone and testosterone shortened the QT interval,[13] thus having a protective effect in patients with LQT1 and LQT2. The lack of sex-specific differences with QTc interval durations and SCD risk between male and female patients with LQT3 can be explained, at least in part, by the fact that estrogen, the main hormone driving the increased risk of TdP in female patients with LQTS, modulates principally I_{Ks} and I_{Kr} and to a much lesser degree I_{Na}, the current affected in LQT3.[13]

Table. Effects of Sex Hormones on Cardiac Electrophysiology and Risk for Sudden Cardiac Death (Table view)

Sex hormone	Effect on cardiac ionic currents					Change on ECG	Risk of sudden cardiac death
	$I_{Ca,L}$	I_{Ks}	I_{Kr}	I_{K1}	I_{to}		
Estrogen	↑	↓	↓↑*	–	↓	↑QT interval	↓BrS and ↑LQTS
Progesterone†	↓	↑	–	–	–	↓QT interval	↓LQTS
Testosterone	↓↑‡	↑	↑	↑	↑	↓QT interval	↑BrS and ↓LQTS

BrS indicates Brugada syndrome; $I_{Ca,L}$, L-type Ca^{2+} current; I_{K1}, inward rectifier K^+ current; I_{Kr}, rapid component of the delayed rectifier K^+ current; I_{Ks}, slow component of the delayed rectifier K^+ current; I_{to}, cardiac transient outward K^+ current; and LQTS, congenital long-QT syndrome.

* Estrogen blocks the hERG channel (I_{Kr}) directly but conversely increases I_{Kr} via enhancing hERG membrane trafficking.

† Progesterone here indicates endogenous progesterone.

‡ Testosterone acutely suppresses $I_{Ca,L}$ directly, whereas in the long term it activates nuclear receptor–mediated pathways for $Ca_V1.2$ channel ($I_{Ca,L}$) expression.

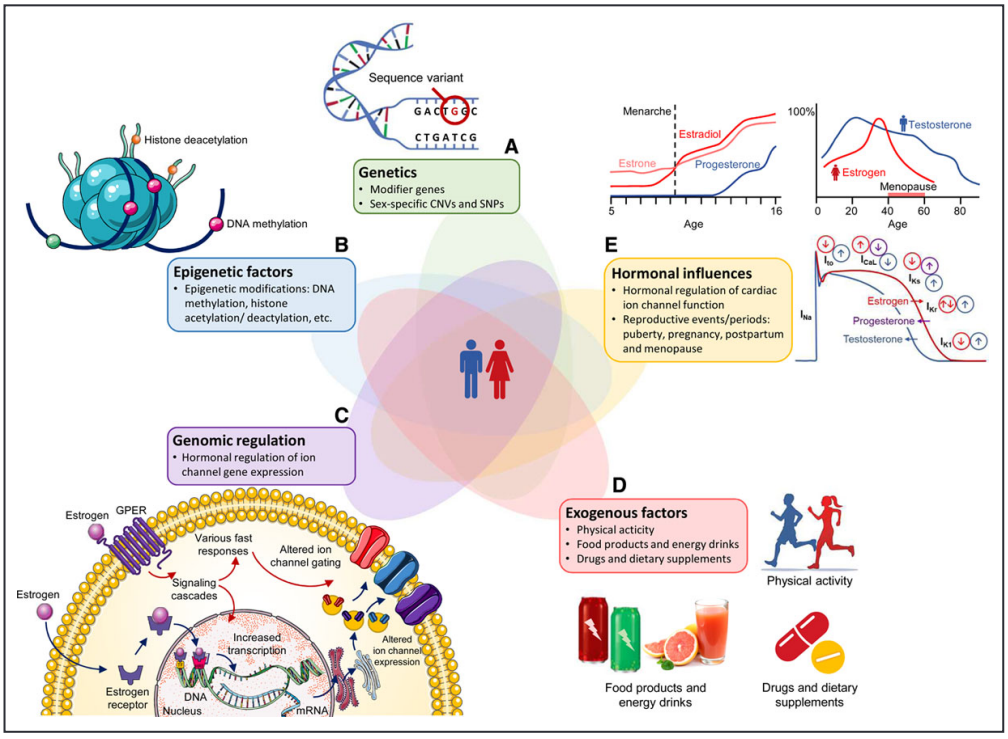

Figure 4. **Schematic representation of the complex interplay of factors that determine the sex-related differences in cardiac channelopathies. A**, The genetic components that contribute to the phenotype of cardiac channelopathies include sex chromosomes, genetic variation (single-nucleotide polymorphisms [SNPs] and copy number variants [CNVs]) and de novo variants. **B**, Sex-related differences can exist in the DNA accessibility and methylation status because of different epigenetic modification patterns. **C**, Sex-specific differences exist in the levels and patterns of gene expression. Regulation of cardiac ion-channel gene expression by sex hormones is an example. For simplified presentation, only the effects of estrogen are shown. **D**, Differences in exposure to exogenous factors such as physical activity, food products, medications, and dietary supplements can contribute to the sex-related differences in cardiac channelopathies. **E**, Sex hormones have significant direct and indirect influence on cardiac electrophysiology in healthy humans and in patients affected by cardiac channelopathies. Female and male sex hormones can enhance or alleviate the arrhythmogenic potential at different ages and reproductive phases. GPER indicates G-protein–coupled estrogen receptor.

Sex-related differences in LQTS have been studied in several animal models. In LQT1 rabbits, no sex differences were present in QT duration, whereas in LQT2, sex differences similar to those seen in humans were present.[37] Female LQT2 rabbits showed a steeper QT/RR relationship, resulting in longer QT duration at slower heart rates.[38] As in patients with LQT2, in transgenic LQT2 rabbits, ventricular arrhythmia and SCD often occurred in the postpartum period.[37,39] In these models, estradiol increased the incidence of lethal TdP arrhythmias by changing the pattern of action potential duration dispersion and increasing early afterdepolarization formation during sympathetic stimulation. Progesterone had an antiarrhythmic effect that was based on shortening of cardiac refractoriness, reduced formation of early afterdepolarization, and stabilization of Ca^{2+}-related effects (decreased $I_{Ca,L}$ density, increased SERCA expression).[39] Studies investigating the effects of postpartum-related hormones oxytocin and prolactin on cardiac electrophysiology in LQT2 rabbits demonstrated a proarrhythmic QT/action potential duration prolongation of both hormones attributable to I_{Ks}-blocking properties.[40]

Management

Although therapy with β-blockers should be offered in both boys and girls on diagnosis, it should be noted that asymptomatic preadolescent boys with a QTc duration >500 milliseconds exhibit a >12-fold increase in the risk of life-threatening cardiac events compared with the respective girls; this indicates the importance of urgent initiation of therapy in these patients.[41] In selected cases, asymptomatic adult men with LQTS, particularly those with older age at diagnosis and QTc <470

milliseconds, may benefit from β-blocker dose reduction (or even discontinuation),[42] considering the lower risk observed at this age[7] and the well-recognized dose-dependent side effects of β-blockers. Female patients, however, might have increased risk after puberty and need attentive evaluation for more aggressive therapy, given the increased QTc duration mediated by the influence of sex hormones.

All patients with LQTS, but particularly those with LQT2, should consider K^+ supplementation. In those with significant and frequent decrease in K^+ levels, therapy with K^+-sparing diuretics such as aldosterone can be a useful add-on therapy. β-Blockers (particularly nadolol) are the mainstay of therapy in LQTS.[1] Therapy with β-blockers is generally effective, particularly in those with LQT1, in whom they are virtually curative, but also in LQT2 with a 70% to 80% efficacy.[11] Response to β-blockade varies by sex and genotype; adult men with LQT1 have the greatest QTc shortening on treatment with β-adrenoceptor blockade.[43]

In LQT3, β-blocker therapy has been reported to result in an 83% reduction in cardiac events in women but not in men (who, however, had many fewer events).[33] Individuals with poor adherence to β-blockers may benefit from a left cardiac sympathetic denervation. Alternatively, mexiletine can be used in patients with LQT3, particularly if they are symptomatic or exhibit a QTc > 500 milliseconds despite β-blockade.[44,45] Limited evidence suggests that flecainide therapy is safe and effective in LQT3; it can be used as an alternative therapy unless patients exhibit flecainide-induced Brugada pattern, which is relatively common in men.[46] Implantable cardioverter-defibrillators (ICDs) are recommended for survivors of cardiac arrest and for patients at high-risk for SCD.[1]

In women with LQTS, until more data become available, the possible QTc-prolonging effect of synthetic progesterone should be considered in decisions on the mode of contraception.[47] Men with LQTS should be evaluated for low serum testosterone levels, androgen deprivation therapy exposure, and endocrine disorders associated with hypogonadism because these factors have been associated with higher risk for drug-induced TdP[48,49] and might represent modifiable risk factors in men with congenital LQTS. A recent small placebo-controlled study showed that transdermal testosterone attenuates the QT-prolonging effects of ibutilide in older men, suggesting that androgens might be useful to prevent or treat TdP in men with drug-induced LQTS.[50] Whether these results have relevance to congenital LQTS remains to be investigated.

Pregnancy

Women are at a decreased risk of cardiac events during pregnancy, particularly those with LQT1.[51] The risk for arrhythmic events, however, is elevated in the postpartum period, especially in patients with LQT2.[51] After the postpartum period, the risk of LQTS-related arrhythmias decreases, returning to the prepregnancy baseline.[51] β-Blockade mitigates the risk of arrhythmias during pregnancy and the high-risk postpartum period.[51] Whereas nonselective β-blockers are recommended for the postpartum period, metoprolol has the most fetal safety data.[52] Broader safety data on propranolol and the limited evidence for its safety in pregnancies in women with LQTS[53] suggest that it might be the best option given its higher efficacy in LQTS. This disparity in the safety of metoprolol and efficacy of nonselective β-blockers (nadolol and propranolol) is not resolved, with good experience by the authors with nonselective β-blockers.[54] In general, β-blockers are well tolerated during pregnancy and the postpartum period with slightly lower fetal birth weights. β-Blockers are secreted in breast milk, so fetal hypoglycemia is an uncommon consequence of maternal β-blocker administration.

Mothers with LQTS have an 8-fold increased risk for stillbirth (fetal death at >20 weeks' gestation; 4% versus 0.5%) and a 2-fold higher risk for miscarriages (fetal death at ≤20 weeks' gestation; 16% versus 8%) than the general population.[55]

BRUGADA SYNDROME

Brugada syndrome (BrS) is a genetic arrhythmia syndrome characterized by coved-type ST-segment elevation followed by a negative T wave in the right precordial leads (V_1–V_3), either spontaneously or provoked by a sodium channel blocker, and increased susceptibility to SCD attributable to polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).[56] Although 21 genes have previously been reported in association with BrS,[20] a recent evidence-based reappraisal of gene-disease validity disputed the causality of 20 genes, leaving *SCN5A* as the only gene with definite causality in BrS.[57] Variants in *SCN5A* underlie 20% of all BrS cases.[58]

Sex-Related Differences in Clinical Phenotype

Although both sexes are theoretically at similar risk to carry variants that predispose to BrS, clinical disease expression is 8 to 10 times higher in men (Figure 3).[59] Because of the overwhelming predominance of men among those with BrS, few data exist on sex differences in disease phenotype. It is recognized, however, that women with BrS are more frequently asymptomatic at the time of diagnosis and 6 to 7 years older than men both at the time of diagnosis (49 years versus 43 years) and with first arrhythmic event (50 years versus 43 years).[25,26] Female patients with BrS less frequently have a spontaneous type 1 Brugada ECG pattern (22%–41% versus 36%–69%) or ventricular arrhythmia inducibility at electrophysiology study (27%–36% versus 42%–66%).[26,60] Moreover, women are 3 to 4 times less likely to experience arrhythmic events, namely syncope, aborted cardiac arrest, and documented VF, than their male counterparts.[26,61] An exception to the male-predominant arrhythmic risk is the pediatric age group, in which a spontaneous BrS ECG was shown to be associated with earlier onset of arrhythmic events—in particular, associated with fever—in girls compared with boys.[60] Therefore, although the age at first arrhythmic event is normally distributed in men, the female distribution is bimodal.[25] It remains unclear whether sex distinction also extends to risk/prevalence of atrial arrhythmias, particularly atrial fibrillation. Studies on atrial fibrillation incidence in BrS included mostly men, but this might be attributed to the male predominance of BrS.

Sex-Specific Risk Factors for Arrhythmic Events

Risk stratification in BrS is difficult, particularly in women, because most data available are based on assessment of men with BrS. Recently, studies with a significant proportion of women with BrS have been published. A pooled analysis of 3 large studies suggests that women make up nearly 28% of all patients with BrS, although some patients may have been included in >1 registry.[24–26] One of these studies, a report on 1613 patients with BrS (31% female), found fragmented QRS and QRS duration >120 milliseconds to be significant predictors of arrhythmic events in female patients with BrS (hazard ratio, 20.2 and 4.7, respectively), incremental to common risk factors such as proband status, history of syncope, and sudden cardiac arrest (hazard ratio, 10.15, 6.8, and 69.4, respectively).[26] These findings are remarkable particularly in the context of a recent study that showed a higher prevalence of *SCN5A* pathogenic variants in asymptomatic female patients with BrS than male patients (27% versus 21%) and a further high prevalence in female

patients with BrS with arrhythmic events compared with male patients (48% versus 28%),[60] suggesting that the presence of an *SCN5A* pathogenic variant in female patients may be a marker of higher arrhythmic risk. In addition, an earlier study found longer PR intervals to be an indicator of arrhythmic risk in female patients with BrS despite similar PR durations in both sexes (hazard ratio, 1.03 per each millisecond of increase).[61] Conduction disturbances are not uncommon in patients with BrS and can be attributed to loss-of-function *SCN5A* variants, which underlie the most identifiable genetic forms of BrS and progressive cardiac conduction disease. Certain *SCN5A* variants such as Gly1406Arg can produce a BrS phenotype in men and isolated conduction disease in women.[62]

Sinus node dysfunction (sinus bradycardia, sinus arrest, or junctional escape) occurs in 1% of men and women with BrS.[26] Some familial BrS-associated *SCN5A* variants produce almost exclusively VF/SCD in men but predominantly sick sinus syndrome and rarely VF/SCD in women.[63] Because VF in patients with BrS is almost entirely during sleep, it has been proposed that arrhythmogenicity in BrS may be related to bradycardia resulting from increased vagal tone or other contributing factors. Thus, concomitant sinus node dysfunction could hypothetically increase the risk for an unfavorable outcome. Although a previous study supported sinus node disease as an arrhythmia predictor in female patients with BrS,[24] a recent analysis of a larger cohort refuted this association in a multivariate analysis model.[26] This highlights the need for refinement of BrS risk stratification, partly explained by the uncertainties about the mechanisms of arrhythmogenesis.

Mechanisms Underlying Sex-Related Differences

Two potential mechanisms of BrS are widely discussed in the literature: (1) depolarization disorder hypothesis, which suggests conduction delay in the right ventricular outflow tract (RVOT) as part of the mechanism of BrS and is more supported by clinical data; and (2) repolarization disorder hypothesis, which is based mainly on evidence of nonuniform abbreviation of right ventricular epicardial action potentials in canine hearts (for details, see Figure 5).[64] Accordingly, potential mechanisms underlying the striking sex-related disparities in BrS might be complex with the interplay of RVOT conduction slowing, differential ion channel expression in endocardium and epicardium, and nonuniform epicardial action potential shapes, which may create an arrhythmogenic milieu. Postmortem histopathological examination and in vivo studies showed increased collagen in hearts from male patients with BrS compared with hearts from male control subjects.[65] In particular, male patients with BrS were found to have epicardial surface and interstitial fibrosis and reduced gap junction expression in the RVOT.[65] Given the more predominant I_{to} in male right ventricular epicardium,[66] this might at least in part explain the male predominance of BrS.

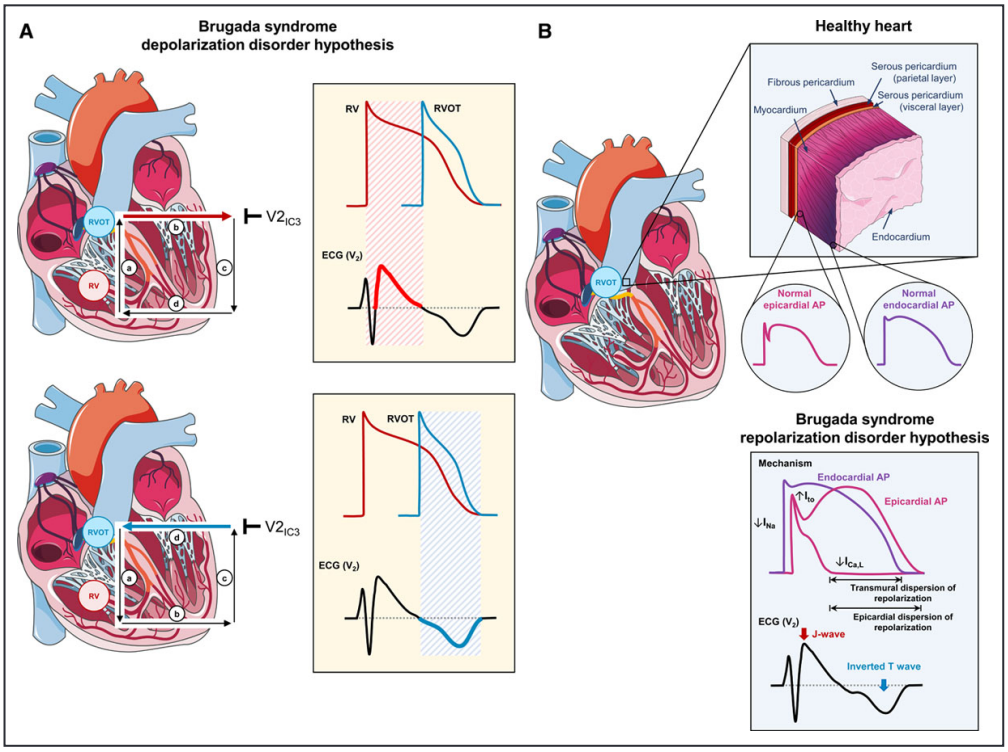

Figure 5. **Schematic representation of proposed mechanisms underlying BrS. A**, Depolarization disorder hypothesis. According to this hypothesis, the Brugada electrocardiographic pattern results from conduction delay in right ventricular (RV) outflow tract (RVOT) with respect to the RV. During the hatched phase of the cardiac cycle, the membrane potential in RV is more positive than in RVOT, driving intercellular current to RVOT (top, a). In a closed-loop circuit, current passes back from the RVOT to RV in the extracellular space (top, c), and an electrocardiographic electrode positioned over the RVOT ($V2_{IC3}$) inscribes a positive signal (bold red line), as it records the limb of this closed-circuit that travels toward it (top, b). Reciprocal events are recorded in the left precordial leads; current flowing from the extracellular space into RV (top, d) causes ST-segment depression. After the upstroke of the delayed action potential (AP) in RVOT, the potential gradients between the RV and RVOT are reversed; membrane potentials are now more positive in the RVOT than RV. This drives the closed-loop circuit in the opposite direction (bottom panel), with current now passing away from lead $V2_{IC3}$ (bottom, d), thus resulting in the negative T wave (bottom, bold blue line). When the RV and RVOT are electrically well coupled, the delayed AP of the RVOT is abbreviated compared with the RV AP; this accelerates repolarization of the RVOT AP (the mass of RV strongly exceeding that of RVOT). **B**, Differences between the epicardial and endocardial APs of the RV/RVOT in healthy hearts, and AP changes underlining the ECG manifestation of Brugada syndrome (BrS) (bottom). The repolarization disorder hypothesis of BrS evolves around the higher expression of I_{to} in epicardium than in endocardium. Because I_{to} is responsible for the early repolarization, stronger I_{to} in the epicardium than endocardium renders the epicardium susceptible to the effects of reduced depolarizing force. Hence, when I_{Na} is reduced as a result of Na^+ channel variants, a “spike-and-dome” shape of the AP arises in the epicardium. Prolongation of the epicardial AP dome leads to longer AP durations in the epicardium than in the endocardium, which accounts for the negative T wave on the surface ECG. With further I_{Na} reduction, I_{to} repolarizes the membrane beyond the voltage at which L-type Ca^{2+} channels ($I_{Ca,L}$) are activated, resulting in heterogeneous loss of the AP dome in the epicardium. Epicardial dispersion of repolarization results in vulnerability to premature impulses (phase 2 reentry), which can trigger ventricular arrhythmias based on reentry between transmural layers.[64] The unaltered AP shape in the endocardium despite I_{Na} reduction, a prerequisite for this hypothesis, is explained by less I_{to} expression in the endocardium. The presence of electrocardiographic changes in only right precordial leads results from larger I_{to} expression in the right ventricular than left ventricular epicardium, whereas the higher disease prevalence in men is explained by higher epicardial I_{to} density in men.

Sex hormones have also been implicated in sex-related disparity in BrS. Male patients with BrS were found to have higher testosterone levels compared with control subjects.[59] In 2 men with spontaneous BrS, surgical castration for treatment of prostate cancer resulted in normalization of the ECG.[67] The modulatory role of testosterone on repolarization currents, namely I_{to} (increase) and $I_{Ca,L}$ (decrease), and opposing effects by estrogen might contribute to sex-related differences in BrS (Figure 5).[66] Among these concepts, the effect of sex hormones may provide the most reasonable mechanistic explanation for the onset of phenotype distinction at puberty and its

persistence until menopause.[25] However, data supporting these hypotheses are scarce, and the true pathobiology behind this variation is likely to involve an interplay of multiple contributing mechanisms.

Data from animal models of BrS on sex-related differences are scarce. The only study with findings potentially relevant for sex-associated differences in BrS reported that, in mice with heterozygous deletion of *Scn5a*, more severe conduction slowing and cardiac fibrosis are observed in aged males compared with aged females, indicating a potential sex-specific effect on disease phenotype.

Management

Given the low risk of VF in asymptomatic patients with spontaneous BrS ECG (≈1%/y), refraining from therapy is reasonable for well-informed patients.[68] All patients should receive aggressive and immediate treatment of fever and avoid drugs that may induce arrhythmias (a list of drugs is available online).[69] ICDs are recommended in patients with arrhythmic syncope and survivors of cardiac arrest.[56] The low risk for life-threatening arrhythmias (2% versus 5% within 5 years of diagnosis) explains the lower rate of ICD implantation in women compared with men (20% versus 34%).[26] Quinidine has been shown to prevent arrhythmic events in symptomatic patients with BrS[70,71] and should be considered in patients with BrS with recurrent ventricular arrhythmias, patients with BrS with atrial fibrillation, or those with BrS who choose to avoid an ICD.[56] Radiofrequency ablation of the arrhythmic substrate in the epicardium of the RVOT has been investigated mainly in male patients with BrS and appears to reduce arrhythmias in patients with BrS with recurrent VF episodes.[72]

Pregnancy

In a retrospective single-center study including 104 women with BrS with 219 deliveries, not a single life-threatening arrhythmia was observed during the pregnancy or peripartum period.[73]

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a cardiac channelopathy characterized by polymorphic ventricular arrhythmias in the setting of high adrenergic tone.[74] Pathogenic variants in the ryanodine receptor 2 gene (*RYR2*) are responsible for ≈65% of CPVT cases, transmitted in an autosomal dominant manner, whereas variants in the cardiac calsequestrin gene (*CASQ2*), responsible for mainly an autosomal recessive form of the disease, are found in 2% to 5% of the CPVT cases.[1]

Sex-Related Differences in Clinical Phenotype

There appears to be a similar proportion of male and female patients with CPVT (Figure 3).[27] Sex-related differences have been described in *RYR2*-CPVT but appear to be minor. Although it was initially thought that men with *RYR2*-CPVT have a higher risk for SCD,[75] recent data do not support this association, and the risk of arrhythmias seems to be dependent on variant type or location. In a Canadian population, the founder *RyR2*-p.R420W variant significantly affected survival in a sex-dependent manner, showing earlier mortality in male patients compared with female patients.[76]

A study that aimed to evaluate the circadian variation of ventricular arrhythmias in pediatric CPVT cases revealed no difference in timing of arrhythmia events.[77]

Sex-Specific Risk Factors for Arrhythmic Events

Large studies found no sex-specific risk factors for SCD in CPVT. The predictors for cardiac and fatal or near-fatal events are younger age at the time of diagnosis and absence of β-blocker therapy.

Management

At present, there are no sex-specific recommendations for management of patients with CPVT. β-Blockers are the standard of care,[1] with nadolol being more beneficial than β1-selective β-blockers. It was recently shown that flecainide added to β-blocker therapy is superior to β-blocker therapy alone for the prevention of exercise-induced arrhythmias in CPVT.[78] Left cardiac sympathetic denervation can be used for patients with drug intolerance or arrhythmias despite medical therapy. Although at present, ICDs are recommended after cardiac arrest in CPVT,[1] recent data suggest that they may cause fatal VT storms, and strict adherence to medical therapy alone may be superior.[79,80]

Pregnancy

A recent study showed that arrhythmic risk in patients with CPVT is not elevated in the combined pregnancy and postpartum period. Events seen were associated with lack of β-blocker therapy and unrelated to pregnancy.[81] Thus, therapy with nonselective β-blockers should continue throughout pregnancy and at least 40 weeks postpartum to alleviate the arrhythmic risk in patients with CPVT.[82]

SHORT-QT SYNDROME

Short-QT syndrome (SQTS) is a very rare, potentially lethal inherited channelopathy characterized by shortened QT interval (QTc <330 milliseconds) on ECG and increased susceptibility to atrial and ventricular arrhythmias and SCD.[83] The disease can also be diagnosed in the presence of a QTc <360 milliseconds and 1 or more of the following: a pathogenic mutation, family history of SQTS, family history of sudden death at ≤40 years of age, or survival of a VT/VF episode in the absence of heart disease.[1] SQTS types 1 through 3 are associated with gain-of-function variants in potassium channel genes (*KCNH2*, *KCNQ1*, and *KCNJ2*, respectively), whereas SQTS types 4 through 6 are caused by loss-of-function variants in calcium channel genes (*CACNA1C*, *CACNB2*, and *CACNA2D1*, respectively).[20] Patients with SQTS may be asymptomatic or present with dizziness, syncope, or SCD, often before 40 years of age.[83]

There is a striking predominance of men (≈70%) among patients with a clinical diagnosis of SQTS, suggesting a sex-dependent penetrance (Figure 3).[28] The reason may be that resting QTc is longer in women than in men, so their QTc intervals are less likely to qualify for the diagnosis. There is, however, no sex-related difference in QTc duration among those diagnosed with SQTS.[28,83] In a pooled analysis of available studies, male patients had a higher likelihood of syncope at first presentation (24% versus 7%) with a similar risk of SCD compared with female patients (24% versus 25%).[28] A composite end point of VT, VF, and SCD was observed more often in female patients (48%) than in male patients (28%), perhaps partly because of the higher detection rate of VT/VF in women, all of whom had ICDs implanted, in contrast with only one-third of men having an ICD.[28] Because of the low prevalence, our understanding of mechanisms responsible for these sex differences remains incomplete.

Because there are no sex-specific risk factors for SCD, sex-specific recommendations for therapy do not exist. Because of the high rate of SCD in patients with SQTS, ICD implantation is the cornerstone of therapy. ICD implantation is indicated in patients with sustained VT or VF and can be considered in patients with a strong family history of SCD.[1] Quinidine has been shown to reduce the incidence of arrhythmias and therefore might be considered in asymptomatic patients with SQTS.[84] Sotalol may also be used for therapy, although fewer data supporting its efficacy are available.[1]

Studies on transgenic SQTS rabbit models, generated by overexpression of the human gain-of-function variant N588K in HERG/*KCNH2*,[85] showed a clear recapitulation of the human phenotype. No sex differences have been observed in QT duration, VT/VF incidence, or SCD rates.[85]

SEX-RELATED DIFFERENCES IN THE PATHOGENESIS AND RISK OF SUDDEN ARRHYTHMIC DEATH SYNDROME

Sudden arrhythmic death syndrome (SADS) is defined as SCD in which both autopsy and toxicology investigations are inconclusive, the heart is structurally normal at gross and histological examination, and noncardiac causes are excluded.[82] The prevalence tends to be higher in younger subjects with SCD. In a Canadian study of individuals with SCD ≤19 years of age, 60% had no identifiable cause of death.[86] In general, the prevalence is higher in men, with varying predominance in different age groups (Figure 6).[87] A study of 967 consecutive cases of SADS showed a male predominance (61%) most evident in the younger age group.[88] The mean age was significantly lower in men (30±12.2 years versus 33.5±15.4 years). Circumstances of death were different between men and women. Although the majority of cases of SADS occurred during rest or sleep, male sex was more often associated with stress- and exercise-related deaths.[88]

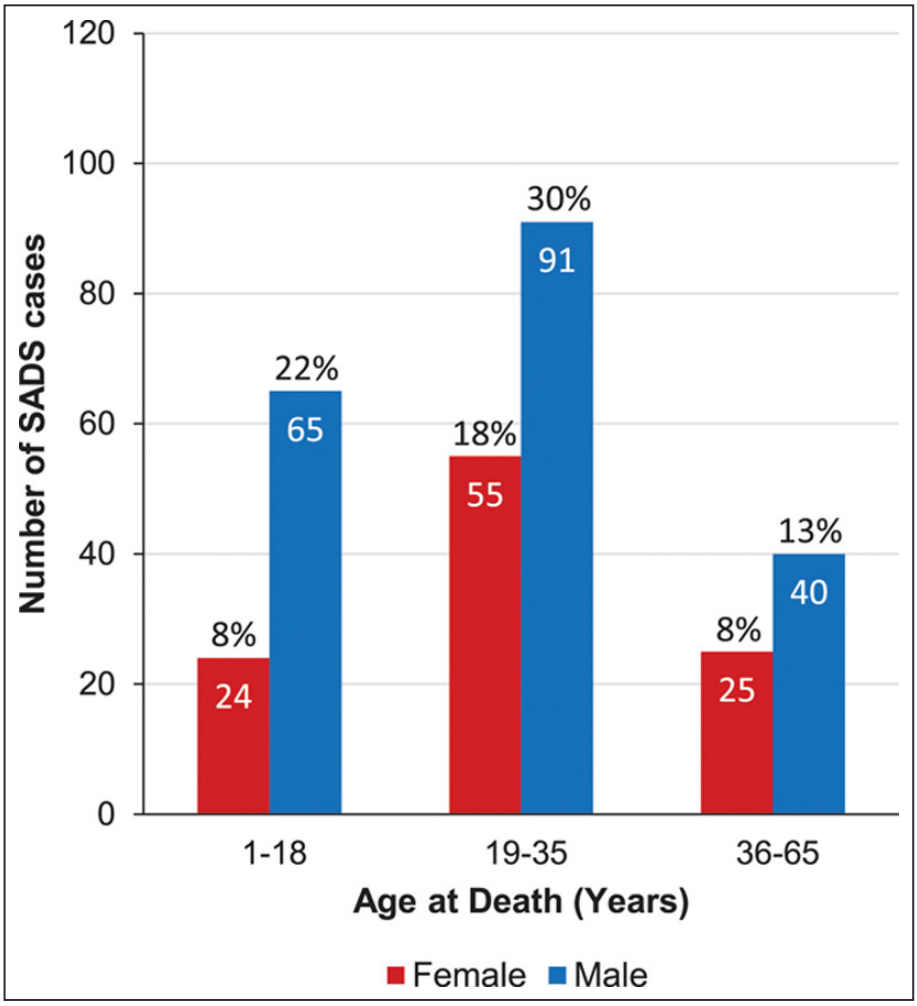

Figure 6. Distribution of cases of SADS among age groups in men and women. Comprehensive postmortem investigation of a large cohort of 302 cases of SADS revealed that SADS more often affected men and individuals ≤35 years of age. The heights of the bars and the counts inside the bars represent the number of cases; the percentages represent the proportion of SADS cases in the respective group in the overall cohort of SADS cases. Reproduced from Lahrouchi et al.[87] SADS indicates sudden arrhythmic death syndrome.

Clinical investigations of surviving relatives and postmortem genetic testing are important tools in the diagnosis of an underlying genetic cause of many cases of SADS, with a combined yield of up to 42%.[87,89] Clinical evaluation often reveals various cardiac channelopathies such as BrS (18% to 28%), LQTS (7%), and CPVT (2%–10%).[87,89] The higher risk of SCD in male children with LQTS and in adult men with BrS compared with female patients in the same age groups might partly explain the higher incidence of SADS in men. Molecular autopsy in SADS has a reported yield of 13% to 32%, depending on the population studies, the testing method, and the thresholds for pathogenicity used.[87] The sex of the subject may also affect the diagnostic yield of the test. For example, a study of 173 cases of SADS (38% women) referred for molecular autopsy showed a higher yield of pathogenic variant detection in women.[90] Among LQTS genotype-positive cases, 68% were women. In contrast, there was a higher proportion of men among *RYR2* (CPVT1) genotype-positive cases (55%), and they tended to be younger. This sex-age correlation of *RYR2* cases was confirmed in a later study.[87]

Little is known about sex differences among surviving family members of subjects with SADS other than early data suggesting that more female relatives attended clinical evaluation than male relatives[5] and that after LQTS-related deaths the mothers are most likely to be the gene carrier.[91] This suggests that epigenetic factors such as imprinting may cause transmission distortion of LQTS genes.[92,93]

GENERAL CONSIDERATIONS FOR PREGNANT WOMEN WITH CARDIAC CHANNELOPATHIES

Because cardiac channelopathies commonly manifest in adolescence or early adulthood, it is not uncommon for physicians to deal with the challenge of pregnancy and the postpartum period in women with cardiac channelopathies. The current approach to pregnant women with a cardiac channelopathy includes identification of high-risk features, avoidance of arrhythmia triggers, preventive therapy when needed, and neonatal screening when possible. Between 5% and 10% of all sudden infant death syndrome cases are attributed to cardiac channelopathies.[94] In general, infants are at low risk of cardiac events during infancy from channelopathies inherited from their parents, but they should nonetheless be screened appropriately.

Unassisted vaginal delivery may be performed in women with cardiac channelopathies. It is advisable, however, to individualize the delivery plan according to the maternal risk profile; in particular, a history of arrhythmias should be taken into account. In patients considered to be at high risk for malignant ventricular arrhythmias, availability of a cardiologist or an electrophysiologist and use of maternal cardiac telemetry during labor are advisable. Anesthetic planning should include reviewing the list of medications that may potentially provoke arrhythmias to avoid drug-induced adverse reactions. For example, anesthetic drugs that prolong cardiac repolarization are strongly discouraged in patients with LQTS.[38] In a series of 57 high-risk patients with BrS undergoing ICD implantation, the injection of a single bolus propofol for induction of anesthesia was safe, with no adverse events noticed during the procedure or the recovery phase.[95] The authors cautioned, however, about the potential of higher risk for BrS-related arrhythmias associated with the use of higher doses of propofol and longer infusions.[95]

Arrhythmic events during labor seem to be very rare. In some cardiac channelopathies such as LQT1, LQT2, and CPVT, arrhythmias are more likely to be provoked by increased heart rate during exertion.[1] The highest heart rates during labor are observed in the active pushing phase. It is notable that heart rate increases more in those receiving intravenous oxytocin. Moreover, oxytocin prolongs cardiac repolarization and can predispose patients with LQTS to TdP arrhythmia and thus should be used with caution during labor.

CONCLUSIONS

Emerging data strongly support the presence of clinically relevant sex differences in the prevalence, risk profile, and clinical course of several cardiac channelopathies. These differences likely result from myriad influences, extending from altered gene expression to hormonal effects, which, however, are insufficiently explored. Sex-specific neural stress response and psychosocial factors may also affect the outcome of cardiac channelopathies and warrant investigation. To address our current gaps in mechanistic understanding, awareness of biological sex as a modifier of cardiac channelopathy phenotype warrants further investigation. The sex-specific roles of steroid hormones in the expression and function of mutant cardiac ion channels needs to be evaluated in animal and human models. Epidemiological data on female and male patients at different ages are essential to understand how individual risk of life-threatening arrhythmias in different cardiac channelopathy genotypes varies over time. Attention should be paid to the incidence of arrhythmic events during phases of major hormonal transitions (such as puberty, pregnancy, postpartum period, menopause) to refine our knowledge of hormonal influences on pathophysiology of cardiac channelopathies. Combining lessons learned from basic and clinical

research may help target different pathogenic mechanisms to prevent fatalities at specific phases in life. Overall, recognition of sex-related differences in cardiac channelopathies along with improved mechanistic understanding of these disparities will likely translate into more personalized patient care, leading to improved clinical outcomes of patients with cardiac channelopathies.

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