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Current Knowledge

Sex-Specific Aspects of Cardiac Electrophysiology and Arrhythmias

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Introduction

We find an increasing awareness of sex-specific aspects in medicine in general and in cardiovascular medicine specifically, where the male prototype and norms dominated for a long period of time. Incidence, aetiology and clinical treatment of arrhythmias are

largely influenced by biological sex. Moreover, there are important sex- and gender-differences in access and response to arrhythmia therapies. In 2018, a consensus document of the European Heart Rhythm Association (EHRA), endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm So-

ciety dedicated to sex-differences in cardiac arrhythmia was released [1]. The document provides a detailed overview of sex-differences in the pathophysiology, epidemiology and management of cardiac arrhythmias. It also emphasises the importance of equal management between sexes if supported by evidence. This article is largely based on the above-mentioned consensus document and is meant to provide a condensed but comprehensive summary of the latest knowledge of sex-specific aspects of arrhythmias.

In earlier publications, “sex” and “gender” were used interchangeably whereas in more recent articles these terms are used more appropriately. The term “sex” is used to differentiate between biological determined characteristics of women and men, whereas

Abstract

This article provides a condensed but comprehensive summary of the latest knowledge of sex-specific aspects of arrhythmias. Starting with sex-based differences in electrophysiological properties of the heart, it further covers sex- and gender-differences in supraventricular tachycardia, atrial fibrillation, ventricular tachycardia and selected inherited cardiac arrhythmias.

Keywords: Arrhythmia; sex difference; gender

“gender” refers to socially constructed characteristics and different behaviour of women and men.

Sex Differences in Electrophysiological Properties of the Heart

Women tend to have shorter PR- [2], atrio-ventricular (AV) and His-ventricular (HV) intervals [3] and marginally shorter rate-corrected QRS-durations than men [4]. The difference in intra-ventricular conduction time seems to be only partly explained by the difference in heart size [4]. In contrast, women have longer QT-interval durations at resting heart rates compared to men, even when the known overestimation of Bazett’s correction for this differences due to faster resting heart rates in women was taken into account [5]. There is only a minor difference in the corrected QT-interval (QTc) between prepubertal girls and boys which supports the explanation that longer QT-intervals in women are caused by the effects of sex hormones [5]. After a significant drop of QTc-interval duration in boys starting with puberty, the sex difference is diminishing with age (fig. 1). Figure 2 presents an overview of sex-specific differences in electrophysiological properties of the heart.

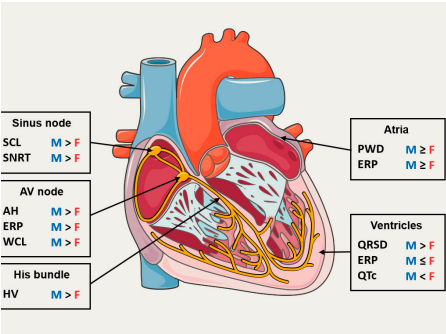


Figure 1: Sex-related physiological differences in electrophysiological parameters. Parameters on the left represent properties of the specialised electrical system. Parameters on the right represent properties of the contractile myocardium. AH: AH-interval; AV: atrioventricular; ERP: effective refractory period; F: female; HV: His-ventricular interval; M: male; PWD: P-wave duration; QRSd: QRS-complex duration; QTc: rate corrected QT-interval; SCL: sinus cycle length; SNRT: sinus node recovery time; WCL: Wenckebach cycle length.

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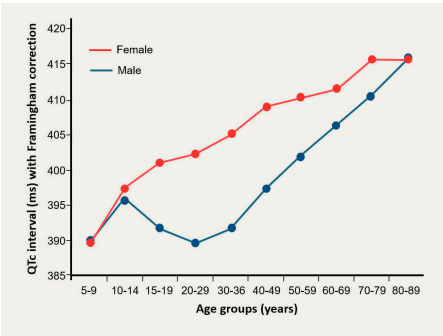


Figure 2: Mean values of rate-corrected QT-intervals in men and women during lifespan. Reproduced from [33].

Effect of the Menstrual Cycle

The menstrual cycle is defined by four phases that are menstruation, follicular, ovulation and luteal phase. The follicular and luteal phase are determined by levels of oestrogen and progesterone. Several studies have linked the hormonal changes during the menstrual cycle to changes in cardiac electrophysiology and in cardiac autonomic status. Unfortunately, the results of these studies have been inconclusive. For example, whereas one study reported a shorter duration of the QT-interval during the luteal phase compared to the follicular phase [6], other studies reported no difference in QT-interval duration over the menstrual cycle [7, 8]. Similar discrepancies exist for other electrophysiological and autonomic parameters.

Certain evidence suggests that women seem to show a cyclic variation of supraventricular tachycardia burden during the menstrual cycle, with more frequent and longer tachycardia attacks in the premenstrual phase or at the onset of menstruation [9, 10]. These findings suggest that atrioventricular-nodal reentry-tachycardia (AVNRT) occurrence, in the presence of dual atrioventricular-node (AVN) physiology may be modulated by sex hormones. A summary of these understudied observations is provided in figure 3.

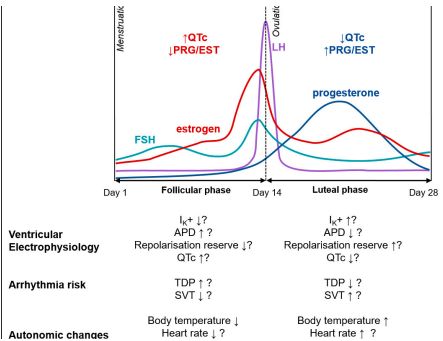


Figure 3: Observed and speculative electrophysiological and arrhythmic changes as response to hormonal changes during menstrual cycle. Question marks indicate previously questioned and

questionable observations, respectively. APD: action-potential duration; EP: electrophysiology; FSH: follicle-stimulating hormone; IKp: delayed potassium rectifier currents; LH: luteinising hormone; QTc: rate corrected QT-interval; SVT: supraventricular tachycardia; TDP: torsade de pointes. Redrawn from [11] with permission from Elsevier.

Supraventricular Tachycardias

Paroxysmal supraventricular tachycardia (SVT) show a sex-dependency varying with the type of arrhythmia. Women have a two-fold risk of developing AVNRT compared to men, although dual AV-node pathway physiology is similar prevalent in men and women [11, 12]. Men show a two-fold higher incidence of accessory pathway (AP) related tachycardia and asymptomatic pre-excitation on electrocardiogram. The location of the AP is sex-dependent, since women have more right-sided AP compared to men. The risk for ventricular fibrillation in patients with pre-excitation is the same for both sexes. The prevalence of focal atrial tachycardia differs between women and men in several studies with some reporting a larger percentage in women and some reporting no difference among the sexes.

The quality of life is affected in all patients with SVT, but women are described to be more symptomatic and to have less quality of life than men [9]. Women presenting with arrhythmia-associated symptoms were more often misdiagnosed as suffering from anxiety, depression or social stress by physicians and are thus referred later for catheter ablation after onset of symptoms. Catheter ablation of paroxysmal SVT is equally safe and successful in women and men [13]. Table 1 summarizes the keypoints of sex-differences in supraventricular tachycardia.

1: Sex-related prevalence of supraventricular tachycardia among women	
intracardiac tachycardia	Sex-related prevalence
atrial tachycardia	F > M
atrial flutter	F = M
atrial fibrillation	F < M
atrial tachycardia	F < M
atrial tachycardia	F > M
atrial tachycardia	F < M
atrial tachycardia	F = M
atrial tachycardia	F > M
atrial tachycardia	F = M
atrial tachycardia	F = M

Atrial Fibrillation

Prevalence and Symptoms

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide. Current estimated prevalence of AF in all adults lies be-

tween 2% and 4% and is increasing with age [14]. The incidence and prevalence of atrial fibrillation are lower in women, when adjusted for age [15, 16]. Women are older at first diagnosis of AF, show a higher prevalence of hypertension and valvular heart disease and a lower prevalence of coronary heart disease compared to men. Women with AF present with more non-ischaemic heart failure and heart failure with preserved ejection fraction [17]. Importantly, women suffer more frequently from thromboembolic stroke, the most feared complication of AF. There are also well described sex-differences in AF-related symptoms, with women being more symptomatic than men and presenting with a higher proportion of more severe EHRA Class III and IV symptoms. Women experience and express more palpitations and fear/anxiety as AF symptoms compared to men. Interestingly, other symptoms (e.g. dyspnoea, chest pain, fatigue) do not show sex related differences. It remains unclear, whether these differences of symptoms arise from biological effects of AF on patients or may reflect a more gender based difference (meaning socio-cultural differences) between men and women in expression of symptoms.

Therapy of Atrial Fibrillation

Women and men with AF are equally likely to receive antiarrhythmic drug therapy [18]. Although women with AF experience more symptoms, it has been reported that women are less likely to receive interventions to maintain sinus rhythm such as cardioversion or catheter ablation. In contrast, women are more likely to undergo primary AV-nodal ablation for rate control. The reason for this imbalance remains unclear. A potential explanation could be that women are older than men at the first diagnosis of AF and show more comorbidities, that women are more reluctant to undergo invasive treatment or are less frequently referred to intervention. It is a matter of debate whether females tend to complain less and therefore are less likely to be considered for an invasive treatment [19]. Unconscious biases and care duties could be other possible explanations for the lower number of women referred to catheter ablation. In 2009 we analysed our own data which showed no sex-related difference in the subsequent treatment decisions for patients once referred to our own specialised outpatient arrhythmia clinic, suggesting that the imbalance in treatment arises at referral-level to the outpatient arrhythmia clinic or even earlier [20]. In a more recent study, we confirmed that the use of pace and ablate strategy was equally chosen

as primary treatment strategy or secondary after prior failed AF ablation for women and men [21]. However, we found significant sex-related differences in the baseline characteristic of these patients. Men were younger, had a lower left ventricular ejection fraction (LVEF), were more often implanted with a cardiac resynchronisation device and had a higher burden of comorbidities. Interestingly, women in our cohort had a more favourable outcome after AV-node ablation, although they were older at the time of pace and ablate treatment.

Women undergoing catheter ablation for AF are significantly older than men [19] which is also supported by our own findings (fig. 4). Other than in the pace and ablate strategy, women show a slightly less favourable outcome after catheter ablation with higher AF recurrence rate. Moreover, they present a slightly higher risk of procedural complications i.e. cardiac tamponade, which is twice as high in women [22]. The less favourable outcome could be partly explained by the fact that women suffer more from non-pulmonary vein mediated AF than men. As the standard approach to treat AF by catheter ablation is pulmonary vein isolation (PVI), the source of some women's AF might not be addressed by this approach. However, non-pulmonary vein mediated AF can be more challenging to map and treat with intervention.

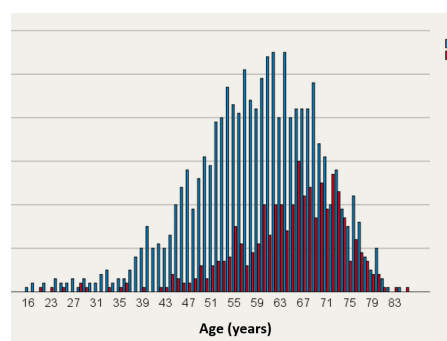


Figure 4: Age distribution of patients having undergone catheter ablation for atrial fibrillation at Inselspital, University Hospital Bern, between 2001 and 2020 (unpublished data).

To summarize, there are three main findings regarding sex differences in catheter ablation for atrial fibrillation: First, women are older than men when presenting for AF ablation. Secondly, women tend to show less favourable outcome to AF ablation. Thirdly, women have a higher risk for periprocedural complications.

Ventricular Tachycardia (VT)

Idiopathic Ventricular Arrhythmias

Idiopathic ventricular arrhythmias are defined as ventricular arrhythmias in the absence of clinically apparent structural heart disease (SHD) and usually have a benign course [23]. Idiopathic ventricular arrhythmias mostly present as frequent premature ventricular complexes (PVC) and/or non-sustained ventricular tachycardia (NSVT). They are subdivided according to their site of origin i.e. right or left ventricular outflow tract (RVOT, LVOT), left ventricular intra-fascicular (verapamil-sensitive) and perimetric or peri-tricuspid. There is a clear sex-related difference in the origin of idiopathic ventricular arrhythmias: RVOT-VT is twice more common in women whereas left ventricular intra-fascicular VT is three times more common in men [24]. The reason for these differences is unknown. Catheter ablation of idiopathic VT is equally effective for women and men and the procedural risk of complications does not differ [25].

Ventricular Arrhythmias Associated with Structural Heart Disease

Sustained VT are mostly related to underlying structural heart disease, due to scar related reentry mechanisms, reentry mechanisms involving an impaired conduction system or due to focal myocardial activity [26].

Of patients with structural heart disease undergoing catheter ablation, women are more likely to suffer from non-ischaemic cardiomyopathy (NICM). Women are younger than men at the time of ablation, present a more preserved left ventricular ejection fraction and show less comorbidities. Despite the more favourable baseline characteristics, women have a worse VT-free survival rate after catheter ablation, even after adjustment for the higher prevalence of NICM [27]. Possible explanations for a higher VT recurrence rate in women may be differences in referral pattern, differences in arrhythmia substrate or undertreatment during ablation. However, since women are largely underrepresented in VT ablation studies of patients with structural heart disease, further studies are needed to get more insights to sex and gender differences.

Inherited Cardiac Arrhythmias

Inherited arrhythmia syndromes (IAS) can lead to sudden cardiac death in the absence of structural heart disease. They are caused by

pathogenic variants in genes coding for cardiac ion channels or associated proteins.

Long QT Syndrome

Long QT syndrome (LQTS) is an electrical disorder characterised by a prolonged repolarisation phase of the cardiac action potential. It is characterised by a prolonged QT-interval on the surface electrocardiogram (ECG). LQTS leads to a predisposition to arrhythmias, including polymorphic ventricular tachycardia (torsades de pointes, TdP), which represents a leading cause of sudden death in the young [28]. As QT-intervals are generally longer in healthy women compared to men, sex is considered an important factor in the management of LQTS patients. Consequently, sex-specific cut-offs for prolonged QT-interval have been determined – 480 ms in women and 470 ms in men [29]. Women have higher disease penetrance than men among patients with disease-causing variants in LQTS-associated genes [30]. Women with LQT1 and LQT2 have longer QTc than affected men [31].

Brugada Syndrome

Brugada syndrome (BrS) is an inherited arrhythmia syndrome characterised by coved-type ST-segment elevation followed by a negative T-wave in the right precordial leads (V1-V3), either spontaneously or provoked by a sodium channel blocker, with an increased susceptibility to sudden cardiac death due to polymorphic VT or ventricular fibrillation. BrS primarily affects men; the phenotype identified 8-10 times more frequently in men. Because of this imbalance, there is a deficit of studies analysing the BrS phenotype and its consequences in women and sex differences are under-investigated. Observational data suggests that women with BrS are more often asymptomatic at the time of diagnosis and 6-7 years older than men, both at the time of diagnosis and at the time of the first arrhythmic event. A potential role of higher testosterone levels in men with arrhythmia has been suggested and is currently under investigation.

Further details on sex-related differences in cardiac channelopathies and their implications for clinical practice can be found in a recent review article [32].

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Conflict of Interest Statement

No financial support and no other potential conflict of interest was reported.

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