Sex-Based Differences in Cardiac Arrhythmias, ICD Utilisation and Cardiac Resynchronisation Therapy

A. Ghani · A. H. E. M. Maas · P. P. H. M. Delnoy ·
A. R. Ramdat Misier · J. P. Ottervanger · A. Elvan

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Abstract Many important differences in the presentation and clinical course of cardiac arrhythmias are present between men and women that should be accounted for in clinical practice. In this paper, we review published data on gender differences in cardiac excitable properties, supraventricular tachycardias, ventricular tachycardias, sudden cardiac death, and the utilisation of implantable defibrillators and cardiac resynchronisation therapy. Women have a higher heart rate at rest, and a longer QT interval than men. They further have a narrower QRS complex and lower QRS voltages on the 12-lead ECG with more often non-specific repolarisation abnormalities at rest. Supraventricular tachycardias, such as AV nodal reentrant tachycardia, are twice as frequent in women compared with men. Atrial fibrillation, however, has a 1.5-fold higher prevalence in men. The triggers for idiopathic right ventricular outflow tract tachycardia (VT) initiation are gender specific, i.e. hormonal changes play an important role in the occurrence of these VTs in women. There are clear-cut gender differences in acquired and congenital LQTS. Brugada syndrome affects men more commonly and severely than women. Sudden cardiac death is less prevalent in women at all ages and occurs 10 years later in women than in men. This may be related to the later onset of clinically manifest coronary heart disease in women. Among patients who receive ICDs and CRT devices, women appear to be under-represented, while they may benefit even more from these novel therapies.

Keywords Gender differences · Supraventricular tachycardia · Ventricular tachycardia · Treatment · Pregnancy · ICD or CRT

Gender Differences in Electrocardiograms

Heart Rate

As early as 1920, Bazett [1] observed that women had a higher resting heart rate than men and this was later confirmed by several other investigators. In a large population-based study ($n=5116$), the average heart rate of women was 3–5 beats per minute faster than that of men [2]. This may partly be explained by differences in body habitus and exercise tolerance, but differences in intrinsic electrophysiological properties of the sinus node and autonomic nervous system may also play a role [3]. Sinus node recovery time is shorter in women. Inappropriate sinus tachycardia is a rare but increasingly recognised clinical syndrome that occurs more frequently in women [4].

QT Interval

Bazett [1] noted that women have a longer QT interval than men, despite their higher heart rates. The mean QT interval in women is about 10–20 ms longer than in men. This difference becomes more marked during the menstruation period, when an enhanced response to drugs has also been reported [4]. The differences in the duration of the QT interval may be at least partially explained by electrophysiological effects of female hormones on calcium and potassium channel function. Female hormones may also affect the length of the QT interval through effects on the fast and persistent sodium current and sodium–calcium exchange [4].

A. Ghani · A. H. E. M. Maas · P. P. H. M. Delnoy ·
A. R. Ramdat Misier · J. P. Ottervanger · A. Elvan (✉)
Department of Cardiology, Isala Klinieken,
Groot Wezenland 20,
8011 JW, Zwolle, the Netherlands
e-mail: v.r.c.derks@isala.nl

The upper limit of the QTc interval in men is 450 ms, whereas in women the upper limit of normal for the QTc interval is 470 ms.

Voltage and QRS Complex Duration

In women, a narrower QRS complex and lower QRS voltage have been reported. This may be attributed to the smaller heart size in women, but is still present after correcting for cardiac mass and body weight. Even with cardiac abnormalities such as ventricular hypertrophy women have a relatively lower QRS voltage compared with men [4].

Changes in Repolarisation

The so-called ‘nonspecific repolarisation abnormalities’ in the 12-lead electrocardiography (ECG) are more frequently present in women. ECG data from 38,000 postmenopausal women who participated in the Women’s Health Initiative show that these repolarisation abnormalities are common and may be a predictor of cardiovascular risk in women after menopause [4].

Gender Differences in Tachycardias of Supraventricular Origin

AV-Nodal Reentrant Tachycardia

AV-nodal reentrant tachycardia (AVNRT) is the most common type of paroxysmal supraventricular reentrant tachycardia. It accounts for approximately 60% of all narrow complex tachycardias seen in clinical practice [5]. AVNRT has a 2:1 women-to-men predominance [4]. A shorter refractory period of the slow pathway has been described in women and may partially explain this higher incidence [6].

Atrioventricular Reentrant Tachycardia

Atrioventricular reentrant tachycardia is the second most common manifestation of paroxysmal supraventricular tachycardias (SVT), which uses the AV node as the antegrade limb and an accessory atrioventricular pathway (AP) for the retrograde limb (these APs can be concealed or manifest with delta wave on surface ECG), is observed twice as often in men as in women (Table 1) [4].

Inappropriate Sinus Tachycardia

Inappropriate sinus tachycardia, which is characterised by an increased resting heart rate accompanied by an exaggerated

Table 1 Summary of gender differences in electrophysiological properties and clinical arrhythmias [7]

Variable	Favours	Details
Electrophysiological properties		
Heart rate	Women	Higher heart rate at rest
QT interval	Women	Longer
Sinus node recovery time	Women	Shorter
Clinical arrhythmia		
Inappropriate sinus tachycardia	Women	
AVNRT common type	Women	2: 1 ratio
AVNRT uncommon type	Women	
Accessory pathways, overt	Men	2: 1 ratio
Accessory pathways, concealed	Men	2: 1 ratio
Atrial fibrillation		
Risk	Men	1.5 times higher
Prevalence	Women	
Complication		
Stroke	Women	2.2 vs. 1.2%, $P=0.011$
Major bleeding events	Women	2.2 vs. 1.3%, $P=0.028$
Successful ablation	Both	2-year freedom from AF: 83.1% women vs. 82.7% men

AVNRT AV nodal reentrant tachycardia

response to exercise or stress, is not associated with underlying structural heart disease. The diagnosis of inappropriate sinus tachycardia is one of exclusion and occurs much more frequently in women, especially below 40 years of age [4, 7]. The aetiology is not fully understood but it is thought to be related to an abnormal autonomic regulation of the sinus node [4, 7].

Atrial Fibrillation

The most common arrhythmia seen in clinical practice today is atrial fibrillation. In the Framingham Heart Study, men were found to have a 1.5-fold higher risk of developing atrial fibrillation compared with women. Atrial fibrillation occurs more frequently in ageing men but does not change in ageing women. The absolute number of women with atrial fibrillation, however, is higher than men because of their longer life expectancy. Men more often have atrial fibrillation after cardiothoracic surgery. Further, women with paroxysmal atrial fibrillation tend to present with longer-lasting episodes and faster ventricular rates [4].

A recent report from the Euro Heart Survey on atrial fibrillation evaluated gender differences in a European population of 5333 patients. Women with AF were older, had a lower quality of life, with more comorbidity, and had more symptoms compared with men [8]. Women also more

often had heart failure (HF) with preserved left ventricular systolic function, and less frequent HF with systolic dysfunction. They more often had risk factors such as hypertension and diabetes with less extensive CAD compared with men. In the Framingham study, it was shown in 5209 subjects that atrial fibrillation was associated with poorer outcomes in women compared with men (OR death 1.5 for men and 1.9 for women) [4, 7]. Moreover, after successful pharmacological or electrical cardioversion, women were more likely than men to have recurrent AF.

Women are treated less aggressively than men for AF, with fewer cardioversions and catheter ablations. In the Euro Heart Survey, similar rates of anticoagulation were found in both men and women; however, at 1 year follow-up, women had significantly higher rates of stroke (2.2% versus 1.2%, $P=0.011$) and of major bleeding events (2.2% versus 1.3%, $P=0.028$) [4, 7]. When antiarrhythmic drugs are used for atrial fibrillation women have a greater risk of QT prolongation and torsades de pointes, as well as more frequent bradyarrhythmias requiring pacemaker insertion [9]. So far, it seems that females are underrepresented in studies of RF ablation. Despite their older age, longer duration of atrial fibrillation, and higher comorbidity the success rate at 2-year follow-up is not different between men and women (82.7% and 83.1%, respectively) with similar complication rates (Table 1) [4, 7].

Menstrual Cycle and SVTs

There is ample evidence that hormones affect the occurrence of SVTs in women. Burke et al. [10] reported that the average heart rate was lower during menstruation than during the follicular or luteal phases of the menstrual cycle. One study evaluated a group of premenopausal women with histories of SVT and followed them with ambulatory monitoring [7]. They found that there were more symptomatic episodes of SVT during the luteal phase of the menstrual cycle, when progesterone levels are elevated. These observations suggest that oestrogen reduces and progesterone enhances the vulnerability to SVTs. Whether this effect is caused by modulation of autonomic tone, direct cellular electrophysiological effects or a combination of both, is unknown. One study noted a cyclic variation in SVT inducibility [7]. Some patients were not inducible during electrophysiological studies performed at mid-cycle but were inducible when the studies were repeated during menstruation.

Arrhythmias During Pregnancy and Postpartum

Atrial or ventricular premature beats are common during pregnancy. They are generally benign and well tolerated.

Patients can usually be reassured and the use of antiarrhythmic drugs is discouraged. During pregnancy and in the postpartum period, women have an additional risk for supraventricular arrhythmias, especially AVNRT. Some studies have reported a fivefold higher risk for new-onset SVT and exacerbations during pregnancy [7]. The causes of this increase are not fully understood, but may be related to hormonal changes, an increased autonomic tone and the rise in intravascular volume. AVNRT can be terminated by vagal manoeuvres or by intravenous adenosine. Prophylactic drug therapy should only be used if symptoms are intolerable or in haemodynamically compromised patients [11]. If prophylactic therapy is needed, digoxin or selective β -blocking agents such as metoprolol are the first choice of therapy, followed by sotalol, flecainide or propafenone [12]. The treatment of focal atrial tachycardia during pregnancy is more challenging due to drug resistance and their associations with structural heart disease. Rate control with β -blocking agents and/or digitalis is crucial to avoid tachycardia-induced cardiomyopathy. The occurrence of atrial flutter and atrial fibrillation is rare during pregnancy and mostly related to structural heart disease. Life-threatening ventricular tachycardias during pregnancy are rare. In healthy patients, idiopathic right ventricular outflow tract tachycardia (RVOT) is the most frequent type, and usually responds to β -blocking agents [13]. Postpartum cardiomyopathy should always be ruled out with echocardiography in women presenting with new-onset ventricular tachycardia during the last 6 weeks of pregnancy or in the early postpartum period. The risk of cardiac arrest in women with the congenital long-QT syndrome (LQTS) is greater in the postpartum period than during pregnancy itself. The relative increase in heart rate in pregnancy shortens the QT interval, and protects against ventricular arrhythmias in these patients [7].

Right Ventricular Outflow Tract Tachycardia

This repetitive monomorphic ventricular tachycardia occurs typically in the absence of structural heart disease and most commonly originates from the right ventricular outflow tract. It is the most common ventricular tachycardia in the patient population under 40 years of age. The triggers for right ventricular outflow tract tachycardia (RVOT-VT) initiation are gender specific. In women the most common trigger is the premenstrual state (hormonal flux), whereas in men it is more commonly initiated by exercise or stress. It has important implications related to patient education and counselling in the setting of RVOT-VT and may influence the timing of drug treatment and electrophysiological evaluation in selected patients [14].

Long-QT Syndrome

Regarding ventricular arrhythmias, there are also clear-cut gender differences in both acquired and congenital LQTS, as well as the risk for sudden cardiac death. In congenital LQTS, there is an unexplained female prevalence of disease. Women are at a higher risk of cardiac events in the period after giving birth, whereas men are more likely to suffer syncope and sudden death until puberty [15]. Acquired LQTS is clinically more common than congenital LQTS and is usually seen with electrolyte abnormalities or the use of medications that prolong ventricular repolarisation. Women exhibit longer QTc intervals and are prone to develop torsades de pointes during administration of some antiarrhythmic drugs. One review reported that women constituted up to 70% of the cases of torsades de pointes, although they accounted for a much lower percentage of antiarrhythmic drug prescriptions [15]. Women are more likely to develop torsades de pointes from antiarrhythmic medications, such as Vaughn Williams class IA and class III (e.g. quinidine and sotalol) antiarrhythmic drugs. However, class IC (e.g. flecainide) do not increase the QT interval and therefore do not increase the risk for torsades de pointes [7].

Brugada Syndrome

Brugada syndrome affects men more commonly and severely than women. Men with Brugada syndrome suffer from sudden cardiac death (SCD) more frequently than women [16, 17]. In a recent prospective study, at inclusion, men constituted the majority of patients (70.8%) and had experienced syncope (18% versus 14%) or aborted SCD (6% versus 1%) more frequently than women. During a mean follow-up of 58 ± 48 months, SCD or documented ventricular fibrillation occurred more frequently in men than in women (11.6% versus 2.8%) [15]. Spontaneous type 1 Brugada ECG has been recognised as a risk factor for SCD in patients with Brugada syndrome. In contrast to men, most women with Brugada syndrome and resuscitated SCD or appropriate ICD shock do not have a spontaneous type 1 ECG pattern. In addition, the degree of ST elevation is less pronounced in women than men. While women represent a lower-risk group overall, risk factors established from a predominantly male population may not be helpful in identifying high-risk females [16].

Gender Differences in Ventricular Tachycardias and Sudden Death

In the Framingham study, the incidence of SCD in women of all age groups was less than half compared with men

[15]. In the VALIANT study, conducted in 14,703 patients with heart failure and ventricular dysfunction after myocardial infarction, 67% of sudden death was seen in men and 33% in women [18]. Other studies on sudden death in patients with ischaemic heart disease confirmed that men have a 50% higher age-adjusted risk of sudden death than women [19]. Women were on average 6–10 years older and this is presumably related to their later onset of coronary artery disease [15]. Further, women with SCD have less obstructive coronary artery disease than men and more often have structurally normal hearts than men [20, 21]. In a retrospective study of 355 survivors of cardiac arrest, obstructive coronary artery disease was seen at coronary angiography in 80% of men and 45% of women [15]. Ventricular premature beats and nonsustained ventricular tachycardia have not been found to predict SCD in women. The inducibility of ventricular arrhythmia with programmed electrical stimulation is different between the two genders. It is easier to induce ventricular arrhythmias in men with postinfarction scarring (95%) than in women (77%). In survivors of cardiac arrest without prior myocardial infarction, ventricular arrhythmias were inducible in only 19% of the women compared with 72% of the men [22]. In the MUSTT trial, the rate of inducibility of sustained ventricular tachycardia was significantly higher in patients with a history of myocardial infarction and in men compared with women [23]. Women with out-of-hospital cardiac arrest present more commonly with asystole and pulseless electrical activity, whereas men usually present with ventricular tachycardia and ventricular fibrillation [15].

Gender Differences in ICD Use and Outcomes

Thus far, women have been underrepresented in studies with the use of implantable devices. In MADIT II, 192 (16%) were women and 1040 (84%) were men. In the COMPANION trial 32% were women and the CABG-Patch trial included only 10% women [15]. The explanation for this disparity may include the lower incidence of sudden death in women, the lower rate of inducibility with programmed electrical stimulation, the appearance of coronary artery disease at older age in women, which in turn might discourage placement of such a device in women [15]. In clinical practice, the use of ICDs is disproportionately low in women. Peterson et al. [15] studied ICD registry data of 160,470 patients and noted that 73% of ICD recipients were male and 27% were female. Another study, which investigated the influence of gender on access to ICD therapy in 353 patients, noted that markedly fewer females received an ICD; the majority, 85%, were male [24].

Adverse Events Related to ICD Implantation

Peterson et al. [15] used the national ICD registry data of first ICD implantation and found that women were more likely to experience any adverse events (4.4% versus 3.3%, $P<0.001$) and major adverse events (2.0% versus 1.1%, $P<0.001$). Despite these gender differences in adverse events, in-hospital mortality after ICD implantation is similar for both sexes.

Benefit from ICD

Davis et al. [24] studied 353 ICD recipients over the mean follow-up of 1.8 years and noted that gender had no influence upon the likelihood of receiving either an appropriate or an inappropriate ICD shock therapy. Russo et al. [25] studied the outcome and arrhythmic events in men versus women in 1,530 patients who received ICD. There were no differences in heart failure hospitalisation, survival or ICD shock therapy during a follow-up of 10.8 months. Chen et al. [26] studied the effect of gender on mortality or appropriate ICD shock in 140 patients with nonischemic cardiomyopathy. They noted that men and women during the follow-up of 30 months had similar rates of appropriate ICD shock therapy (36% versus 38%) and mortality (21% versus 11.5%, $P=0.11$). In controlled randomised ICD trials in patients with coronary artery disease at high risk of ventricular arrhythmia, similar benefits from ICD implantation were seen in both genders [27]. In a substudy of MADIT II, 1232 patients were followed for 2 years and no gender differences in mortality were found in the group assigned to ICD placement [4, 24]. The risk of appropriate ICD therapy for VT/VF was lower in women (OR 0.60; 95% confidence interval (CI) 0.37–0.98; $P=0.039$).

Gender Differences in CRT Use and Outcomes

Cardiac resynchronisation therapy (CRT) has a beneficial effect on clinical symptoms, exercise capacity and systolic left ventricular performance in patients with heart failure [28–30]. The CRT trials, COMPANION, CARE-HF and MADIT CRT, included 25–33% female patients and demonstrated a significant improvement in mortality and decrease in hospitalisations for heart failure in both genders [15, 31].

Benefit from the CRT

There is some conflicting evidence that women may have more benefit from the CRT devices. In the final subanalysis of the MIRACLE trial, Woo et al. [32] reported significant differences in primary endpoints between genders. CRT decreased the likelihood of reaching the combined endpoint of first heart failure hospitalisation or death for women, but

not for men, as compared with their controls. However, in the COMPANION and CARE-HF trials the hazard ratios for the primary endpoints (composite death and/or heart failure hospitalisation) were very similar for both men and women [33, 34]. In a single-centre observational study, Zardkoohi et al. [35] studied the impact of age and gender on CRT outcomes. They reported a similar long-term outcome in both genders. In another study, Bleeker et al. [36] investigated the gender difference in response to CRT. The absolute number of clinical response to CRT was not statistically significant between the genders (80% in male versus 76% in female). The long-term survival did not differ between the two groups at 1 year (86% men vs. 93% women) and at 2 years (80% men vs. 84% women).

In the subanalysis of the recent pivotal MADIT-CRT trial, Moss et al. [32] compared CRT-ICD with ICD-only in relatively asymptomatic heart failure patients and demonstrated that CRT-ICD therapy was associated with a greater benefit in women (hazard ratio, 0.37; 95% CI 0.22–0.61) than in men (hazard ratio 0.76; 95% CI 0.59–0.97; $P=0.01$ for interaction). More studies are needed to answer the question whether women really have more benefit from cardiac resynchronisation therapy.

Conclusion

There are clear gender differences in the incidence and prevalence of cardiac arrhythmias. Women have a higher incidence of AVNRT, whereas men more frequently have accessory pathway-mediated arrhythmias. During pregnancy, AVNRT is the most common arrhythmia. Atrial fibrillation is more prevalent in men in all age groups, but the absolute number of women with atrial fibrillation is higher. Brugada syndrome is more prevalent in men than in women. Women exhibit a longer QTc interval and are more prone to develop torsades de pointes during administration of certain (anti-arrhythmic) drugs. Men have a higher incidence of sudden cardiac death, whereas women with sudden cardiac death are less likely to have a history of coronary artery disease. Despite higher rates of adverse events in women, ICD therapy is well tolerated and provides similar survival benefits for both sexes. The rates of ICD implantation for women appear to lag behind those of men. Only one third of the cardiac resynchronisation therapy device recipients are women despite some recent evidence that women may have more benefit from cardiac resynchronisation therapy.

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