of Cardiology

The effects of gender on electrical therapies for the heart: physiology, epidemiology, and access to therapies

A report from the XII Congress of the Italian Association on Arrhythmology and Cardiostimulation (AIAC)

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Received 19 August 2016; editorial decision 17 February 2017; accepted 18 February 2017; online publish-ahead-of-print 19 May 2017

The difference between men and women is clear even just by looking at an electrocardiogram: females present higher resting heart rate, a shorter QRS complex length and greater corrected QT interval. The development of these differences from pubertal age onward suggests that sexual hormones play a key role, although their effect is far from being completely understood. Different incidences between sexes have been reported for many arrhythmias, both ventricular and supraventricular, and also for sudden cardiac death. Moreover, arrhythmias are an important issue during pregnancy, both for diagnosis and treatment. Interestingly, cardiovascular structural and electrophysiological remodelling promoted by exercise training enhances this 'gender effect'. Despite all these relevant issues, we lack gender specific recommendations in the current guidelines for electrical therapies for heart rhythm disorders and heart failure. Even more, we continue to see that fewer women are included in clinical trials and are less referred than men for these treatments.

Keywords Gender • Sex • Arrhythmia • Review • Defibrillator • Ablation • Exercise • Pregnancy

Introduction

The importance of sex differences in both physiology and pathology dates to the beginning of early research and medicine. Focusing on electrophysiology, at the beginning of the 20th century, Bazett observed that women have a higher resting heart rate than men.[1] Awareness of the importance of gender influence is growing, but many current trials on several pharmacological and non-pharmacological treatments still lack adequate representation of the female population and sex-specific analysis, although their findings are often extended to women in general. In this review, we aim to point out the main gender-related differences concerning the electrophysiological properties of the heart, arrhythmia epidemiology and access to therapies.

Gender and electrical physiology of the heart

Several electrophysiological properties were found to be significantly affected by sex.[2–4] In particular, women present:

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- enhanced sinoatrial node automaticity, independent of the influence of the autonomic system, with shorter sinus cycle length and shorter sinus recovery time, especially during pregnancy[5,6];
- enhanced atrio-ventricular node function: with shorter AH interval and atrio-ventricular node effective refractory period[7];
- faster infra-hisian conduction: with shorter HV interval[6,7];
- longer ventricular action potential duration: occurring in the post-pubertal phase.[4]

The standard 12-lead ECG reflects most of these differences, as shown in *Figure 1*. Women show a 3–5 beats/min higher heart rate at rest.[1,8] This appears to be related to sexual hormone effects, autonomic nervous system influences and the already mentioned intrinsic properties of the sinus node.[5,9] Available data suggest that P wave length is significantly shorter in women (female 118 ± 9 ms, male 122 ± 8 ms)[10] and, as a result of reduced AH and HV intervals, women also show a shorter PR interval.[6] Notably, the two most important ECG findings are the shorter QRS duration and the more prolonged corrected QT (QTc) interval in women.[2–4,11] In prepubertal age, QRS duration lengthens gradually from birth without significant differences between the sexes,[12] but starting from adolescence QRS becomes wider in males (90 ± 12 ms in males, 68 ± 13 ms in females).[6] Lower cardiac mass has been suggested as an explanation, but this difference persists even after correction for body weight and cardiac mass.[13,14]

It has been clearly established that the QTc interval is longer in women,[4,15,16] and this is clinically relevant because a higher QTc interval duration is associated with increased arrhythmic risk, in particular of Torsade de Pointes.[17] Also this difference becomes more evident after puberty.[18] After menopause, the QTc difference between the sexes is negligible.[18] This suggests that sexual hormones play an important role in gender related difference in heart electrical physiology with a particularly evident effect in myocardial repolarization. Indeed, Burke *et al.*[19] showed a different length of QTc interval during the menstrual cycle (shorter QTc interval occurring in the progesterone-dependent luteal phase), only present after double autonomic blockade. However, in the absence of drug-induced autonomic nervous system block, there is no clear evidence regarding QTc interval variation during menstrual cycle.[20,21] Cardiomyocytes possess cell receptors for the three main sex-steroid hormones (oestrogens, progesterone, and testosterone),[22] all of which seem to affect myocardial repolarization: endogenous testosterone and progesterone shorten the action potential, while oestrogens were shown to increase QTc interval duration in animal studies.[23–26] In particular, estradiol's effect on QTc appears to be mediated by down-regulation of the expression of potassium channel currents, such as the slowly activating delayed rectifier current, which play a role in myocardial repolarization.[24] However, these findings have not been replicated in human studies.[26,27] Testosterone-induced QTc interval shortage in males after puberty also contributes to explain QTc interval duration difference between the sexes.[14,26,28]

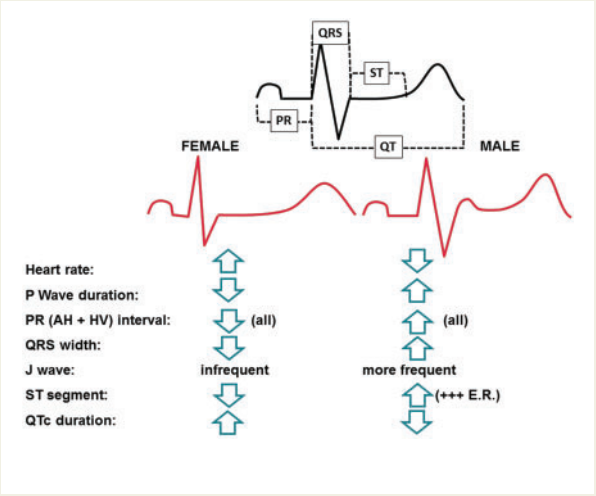

Figure 1 Different gender-related characteristics of cardiac electrophysiology as reflected by surface 12-lead ECG. E.R., early repolarisation.

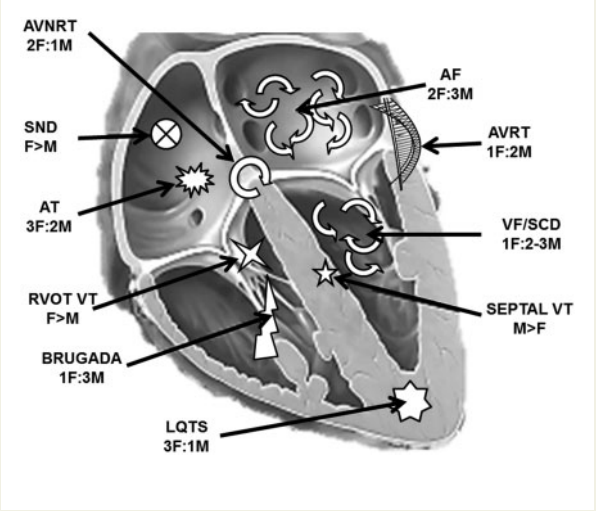

Figure 2 Epidemiological differences in the prevalence of principal arrhythmias between female (F) and male (M) patients. AF, atrial fibrillation; AVNRT, atrio-ventricular node reentrant tachycardia; AVRT, atrio-ventricular reentrant tachycardia; AT, atrial tachycardia; LQTS, Long QT syndrome; RVOT, right ventricular outflow tachycardia; SCD, sudden cardiac death; SND, sinus node disease; VF, ventricular fibrillation; VT, ventricular tachycardia.

Gender and epidemiology of arrhythmias

Evaluation of epidemiological differences of clinical arrhythmias between females and males is a hard task since referral for treatment of these conditions is affected by several factors besides disease occurrence (as discussed below). However, despite the mentioned limitations, available data highlight a different prevalence among females (vs. males) for several arrhythmias (*Figure 2*).[2,13,29,30] In the field of supraventricular tachyarrhythmias, women have a higher prevalence of AV nodal re-entrant tachycardias (AVNRT), and focal automatic tachycardias, while accessory-pathways (both manifest and concealed), with/without atrioventricular re-entrant tachycardia (AVRT) have a greater prevalence in males. Notably, the occurrence of specific episodes of supraventricular arrhythmia may vary with the menstrual cycle, being more frequent in the luteal phase.

Although the reason for this correlation has not been established, hormonal and autonomic factors seem to be involved.[31,32] Similar findings have also been reported for ventricular premature complexes, whose frequency is lower in the ovulation period.[33] Males have a higher prevalence of flutter and atrial fibrillation (AF) at all ages (about 1.5-fold higher risk, *Figure 2*), but since women present an overall greater longevity, doubling the number of living men over 75 years, the prevalence of AF in women is greater than that of men at older age and on the whole is almost equal (53% of all patients with AF according to data from the Mayo Clinic).[34,35]

Some gender-related differences have been reported regarding the prevalence of various idiopathic VTs, with the right ventricular outflow tract VT form more prevalent in women, the left ventricular septal VT form more frequent in men and the left ventricular outflow tract VT form equally distributed.[36] However, the most important findings regard incidence of sudden cardiac death and long-QT syndrome. In general, females present a lower incidence of sudden death both at younger and older age.[37] This can only partially be explained by a lower incidence of structural heart diseases in female subjects: in cardiac arrest survivors and autopsy series, coronary artery disease was found in 45–50% of women vs. 80–90% of men, and at post-mortem evaluation women more frequently presented a structurally normal heart.[37–39] On the other hand, a higher prevalence of female subjects has been reported in long-QT syndrome, both in genetically determined and acquired (drug induced) forms.[16,30] Notably, in inherited long-QT syndrome[40] the occurrence of symptomatic events is higher in boys before puberty, but higher in females later. An evident influence of gender has been reported for Brugada syndrome too: the incidence of typical ECG pattern is more frequent in males (with an 8:1 predominance), while risk of sudden cardiac death or clinically relevant arrhythmia was more than 3 times higher in men than in women.[41,42]

Regarding bradyarrhythmias, in a large, real-life retrospective study women were found to be more likely to undergo pacemaker implantation for sick sinus syndrome than males, while atrioventricular blocks represent a more important indication in men.[43]

Pregnancy and arrhythmias

The most important ECG changes described during pregnancy are an increase of heart rate with reduced heart rate variability and a significant QTc interval lengthening.[44] Pregnancy is a particular condition for arrhythmias too: about 1–4% of pregnant women without structural heart disease will present arrhythmias during pregnancy. However, only a few of these will need specific treatment. While history of previous arrhythmias seems to be the most important predictor of arrhythmia recurrence during pregnancy, there are conflicting data regarding the evolution of the arrhythmic pattern in these patients.[45–47] In some cases, especially in subjects with Wolff–Parkinson–White syndrome, an increase in arrhythmic burden has been reported. The mechanism underlying this arrhythmic burden increase is not fully explained, but likely it is the result of the haemodynamic, hormonal and increased sympathetic tone that occurs in pregnancy.[48] In these subjects, the first step is to exclude any transient cause, especially electrolyte imbalances and thyroid dysfunction (hyperthyroidism may occur in 5–15% of women peri-partum and in 4–8% post-partum). Notably, several factors contribute to the reported symptoms and in up to 90% of the subjects there is no association between symptoms and Holter/ECG findings.[49] Available data suggest that ventricular arrhythmias are unusual during pregnancy in patients without pre-existing heart disease.[2,46] Conversely, patients with known long QT syndrome (Type 1 and 2) present an increased likelihood of arrhythmic event in the post-partum period.[44] The number of pregnant women with congenital heart disease (CHD) is constantly rising, and this group is at particular high risk of arrhythmias during pregnancy.[50] Intrinsic conduction abnormalities, volume overload, persistence of operative scar and impaired autonomic nervous system are the main contributors to the development of heart rhythm disorders.[51] The risk of clinically relevant arrhythmias for women with CHD was reported to be about 4.5% in completed pregnancy, but it is strictly related to the underlying CHD, being the highest for atrioventricular septal defect, post-operative Fontan and corrected tetralogy of Fallot and complete transposition of the great arteries.[52] For patients with CHD, pre-pregnancy counselling is recommended and, in some cases, pregnancy should be discouraged.[53,54]

Gender and cardiovascular response to exercise training

Constant physical activity leads to multiple adaptations, in particular involving the heart and autonomic nervous system, which may become manifest on the ECG. Training-related ECG modifications in athletes include sinus bradycardia and new atrioventricular blocks (mainly first degree and Mobitz 1) and junctional rhythm, early repolarization pattern (ERP), positivity to voltage criteria for left ventricle hypertrophy and right bundle branch block.[55] These changes are less expressed in female athletes: in particular, those concerning QRS criteria for left ventricle hypertrophy and ERP.[55–57] A lower prevalence of partial right bundle branch block and sinus bradycardia has also been reported, but there is conflicting evidence of this finding.[56,57] No significant difference has been described for antrioventricular blocks and junctional rhythm.[56] Interestingly, not only is ERP less frequent in female athletes, but it also seems to be differently represented on the 12-lead ECG. Wafsy *et al.*[57] reported that the higher prevalence of ERP in males was mainly due to an anterior distribution of the ERP on ECG leads, while Junttila *et al.*[58] reported a significant higher prevalence of ERP in the inferior leads in males. These findings are relevant when considered in light of the association between presence of ERP in the inferior leads and incidence of sudden cardiac death in the general population[59] and the increased risk of sudden cardiac death in age-matched athletes,[60] especially males.[61] This is a relevant topic for future studies.

The described differences in ECG morphology among female athletes are probably due to a different expression of heart remodelling in response to exercise training. Male athletes present a more pronounced concentric left ventricular hypertrophy and atrial remodelling[62] coupled with a longer signal-averaged P-wave duration. These findings may represent the substrate for a higher prevalence of atrial fibrillation in male athletes.[63] However, we lack definite data confirming this hypothesis. A recent metanalysis[64] reported that only studies enrolling exclusively male subjects showed a higher incidence of AF in trained athletes, a finding not confirmed in mixed sex reports. However, this evidence is limited by the lack of significance when directly comparing incidence of AF among female and male athletes

Table 1 The main large randomized controlled trials (>200 patients) on ICD implant for primary/secondary prevention of sudden cardiac death with the prevalence of women

Study	Year	Procedure	Inclusion criteria	*N*	F (%)	Mean age (year)	Mean LVEF (%)	Primary endpoint	Average follow-up (mo)	Global outcome	Outcome M/F
ICD as secondary prevention											
AVID[66]	1997	ICD vs. ADT	VF or SVT + syncope/LVEF ≤40%	1016	**21**	65	31.5	Mortality	18.2	ICD > survival (HR 0.62 $P < 0.02$)	Not stratified by gender
CASH[76]	2000	ICD vs. ADT	CArr + documented SVT/VF	288	**20**	58	46	Mortality	57	ICD non-significant > survival (HR 0.77 $P = 0.081$)	Not stratified by gender
CIDS[72]	2000	ICD vs. ADT	VF or syncope + SVT spontaneous or inducible at EP testing or VT + LVEF ≤ 35% and haemodynamic compromise	659	**15**	64	33.8	Mortality	36	ICD non-significant > survival (19.7% RRR, $P = 0.142$)	No significant reduction of primary outcome for both sexes
ICD as primary prevention											
MADIT I[80]	1996	ICD vs. conventional MT	NYHA I-III, prior MI, NSVT + LVEF ≤ 35%, no revascularization	196	**8**	63	26	Mortality	27	ICD > survival (HR 0.46 $P < 0.009$)	Not stratified by gender
MUSTT[70]	1999	ADT and ICD vs. no antiarrhythmic therapy	CAD + LVEF ≤ 40% + NSVT or SVT/VF induced by EP testing	704	**10**	65.5	28	SCD or CArr	39	ICD > survival ($P < 0.001$)	No significant gender difference ($P = 0.35$)[88]
MADIT II[82]	2002	ICD vs. conventional MT	MI 1mo; LVEF ≤ 30%	1232	**16**	64	23	Mortality	20	ICD > survival (HR 0.69 $P < 0.016$)	M:0.66 ($P = 0.011$); F:0.57 ($P = 0.132$). ($P = 0.19$)
DINAMIT[74]	2004	ICD vs. conventional MT	CAD, LVEF ≤ 35% (MI 6–40 days)	676	**24**	61.8	28	Mortality	30	ICD non-significant > survival (HR: 1.08, $P = 0.66$)	No reduction of primary outcome for both sexes
DEFINITE[75]	2004	ICD + MT vs. MT	CHF (NYHA I-III) + LVEF ≤ 35%; NSVT or frequent VEBs on Holter	458	**29**	58.3	21.4	Mortality	29.0	ICD non-significant > survival ($P = 0.08$) < SCD (HR 0.20 $P = 0.006$)	M:0.49 ($P = 0.018$); F: > 1.0 ($P = 0.76$)
SCD-HeFT[68]	2005	MT vs. MT + ADT vs. CMT + ICD	CHF (NYHA II-III) + LVEF ≤ 35%	2521	**23**	60	25	Mortality	45.5	ICD > survival (HR 0.77 $P < 0.007$)	M:0.73 (0.57–0.93); F:0.96 (0.58–1.61)

The female prevalence among enrolled population is expressed in bold.

ADT, antiarrhythmic drug therapy; CAD, coronary artery disease; CArr, cardiac arrest; CHF, chronic heart failure; EP, electrophysiology; F, female; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; M, males; MI, myocardial infarction; MT, medical therapy; N, number of patients; NSVT, non-sustained ventricular tachycardia; RRR, relative risk reduction; SCD, sudden cardiac death; SVT, sustained ventricular tachycardia; VEB, ventricular ectopic beats; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2 The main randomized controlled trials on AF ablation with the prevalence of women

Study	Year	Procedure	Inclusion criteria	*N*	F (%)	Mean age (year)	Mean LVEF (%)	Primary endpoint	Average follow-up (mo)	Global outcome	Outcome M/F
Oral *et al.*[83]	2006	CA vs. ADT for SR maintenance (second-line therapy)	AF for > 6 mo, recurrence within a week of cardioversion	146	**12**	56	55	Freedom from AF/AFL	12	CA > SR maintenance without ADT in 74% of patients ($P = 0.05$)	Not reported
APAF[84]	2006	CA vs. ADT for SR maintenance (second-line therapy)	AF > 6 mo, AF burden > 2 mo in last 6 mo	198	**32.5**	56	60.5	Freedom from recurrent AT	12	CA <AT recurrence (6% vs. 22%; $P < 0.001$)	Not reported
CAFCOAF[85]	2006	CA vs. ADT for SR maintenance (second-line therapy)	Persistent AF, resistant to ADT	137	**37**	62	58.5	Freedom from documented AT	12	CA + ADT reduce AT recurrences ($P < 0.001$)	Not reported
Wilber *et al.*[87]	2010	CA vs. ADT for SR maintenance (second-line therapy)	3 episodes of symptomatic AF within 6 mo, ADT refractory	167	**34**	55	62	Freedom from documented AF	9	CA resulted in a longer time to treatment failure (HR 0.30, $P < 0.001$)	Not reported
MANTRA-PAF[73]	2012	CA vs. ADT for SR maintenance (first-line therapy)	2 symptomatic AF episodes < 6 mo, no episode >7 days	294	**30**	55	Not reported	Burden of AF	24	CA <burden of AF (9% vs. 18%, $P = 0.007$ at 24 mo). No significant difference at 3, 6, 12, or 18 mo	Not reported
RAAFT 2[79]	2014	CA vs. ADT for SR maintenance (first-line therapy)	Paroxysmal AF, symptomatic, no ADT treatment	127	**24**	55	61	AT recurrence	12	CA <rate of recurrent AT (HR 0.56, $P = 0.02$)	Not reported
SARA[78]	2014	CA vs. ADT for SR maintenance (first-line therapy)	Symptomatic persistent AF, refractory to ADT	146	**22**	55	61	Freedom from AF/AFL >24 h	12	CA is superior to ADT for the maintenance of SR ($P = 0.002$)	Not reported

The female prevalence among enrolled population is expressed in bold.
ADT, antiarrhythmic drug therapy; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachyarrhythmia; CA, catheter ablation; F, female; HR, hazard ratio; LVEF, left ventricular ejection fraction; *N*, number of patients.

in studies enrolling mixed sex populations. Notably, a recent report from the EORP-AF Registry showed that physical activity seems not to be associated with arrhythmia progression in patients with a history of AF.[65]

Effects of gender on access to electrical therapies

Several reports[66–90] highlighted a different referral for electrical therapies in male and female subjects (*Tables 1* and *2*), and this behaviour is also observed in common clinical practice and clinical research. Dhruva *et al.*[91] performed a systematic review of 78 high-risk devices, which received premarket approval from the FDA between 2000 and 2007, and showed that 28% of the studies did not report any data on the gender of study participants, while in the remaining cases women, on average, represented 33% of the device recipients. Forty-one percent of the studies presented a specific comment/analysis on sex discrepancies and about one fourth of these analyses showed some sex-related differences in terms of safety/efficacy.

An analysis of the major trials focused on implantable cardioverter defibrillator (ICD) shows a limited prevalence of females among the enrolled subjects (about 20–30%, *Table 1*),[66–72,74–77,80–82,86] that are difficult to explain with mere epidemiological factors. The same occurred for trials involving ablation of supraventricular arrhythmias (*Table 2*).[73,78,79,83–85,87] Similar findings are confirmed in reports from high volume centres and in multi-centre registries. Treatment of AF is a paradigm: women with AF have more comorbidities (especially heart failure with preserved systolic function) and a lower quality of life, but they are more frequently treated with a conservative approach, mainly based on a rate control strategy. This happens despite the fact that catheter ablation could represent an attractive alternative in appropriately selected patients.[92–96] In addition, women are referred for AF ablation later in the course of the disease (e.g. after a longer history of AF, when left atrium dimensions are larger than those observed in men), usually after several failed attempts with antiarrhythmic drugs. They are also older and with more comorbidities (e.g. valvular heart disease, rheumatic disease and hypertension).[93,97,98] Similar data were reported for AVNRT/AVRT ablation, with female candidates referred after a longer use of antiarrhythmic drugs (30% vs. 8%; $P = 0.022$) than males.[99] Notably, women have a twice higher probability than men of undergoing misdiagnosis between SVT and panic disorder,[100] which could contribute to a delay in the diagnosis of arrhythmias.

Moving on to electrical therapies applied in patients with left ventricular dysfunction and heart failure, an imbalance in referral of female vs. male patients is confirmed. Despite the higher prevalence of ischaemic heart disease in male subjects, hospitalization for heart failure is no less frequent in female patients,[101] reflecting a higher prevalence of the disease especially at advanced ages. However, females are under-referred for cardiac resynchronization therapy (CRT), as reported by several authors,[102–104] with the implantation rate being 1–5 for all age classes.[105,106] This gap is also present in the chance of receiving an ICD, and is not limited to acquired cardiomyopathies (with the possible driver of the prevalence of ischaemic heart disease) but also for inherited disease, both in primary and secondary prevention.[107–110] These data were confirmed by a recently published large multi-centre French registry (female prevalence 15.1%),[111] and the Defibrillator Implantation in Patients with Nonischemic Systolic Heart(DANISH) trial (female prevalence 27–28%).[112] Noteworthy, a post hoc analysis of the Antiarrhythmics vs. Implantable Defibrillators (AVID) trial showed a similarly low prevalence of the female sex in both screened and enrolled patients for ICD implantation for secondary prevention (25% vs. 22% $P = 0.313$).[113] This suggests that female underrepresentation in ICD trials may not be due to a 'study-driven' selection bias. The main reasons may belong to a different clinical profile (leading to exclusion by enrolment criteria) or to a general under referral of women for non-pharmacological therapies.

Possible explanations for the under-referral of female patients for device therapy are

(1) longer time to diagnosis;
(2) subject preference for a non-invasive approach;
(3) medical concerns regarding X-ray-related complications;
(4) medical concerns regarding higher chance of procedural complications;
(5) tendency to a less intensive pattern of resource utilization;
(6) higher ratio of heart failure with preserved left ventricular ejection fraction, that may reduce indications for cardiac implantable electrical devices implantation compared to men.[114]

However, this phenomenon has not yet been fully defined. Notably, when looking at the appropriateness of indication, no difference between the sexes has been reported for ICD or CRT implantation.[54,115]

Conclusions

Several aspects of cardiac electrophysiology are influenced by gender. At the 12-lead ECG, females present a higher heart rate at rest, shorter QRS, and longer QTc interval. Incidence of specific arrhythmias and sudden death is also affected by gender, with AVNRT and focal tachycardias occurring more frequently in females while AVRT and atrial fibrillation/flutter and sudden cardiac death are more frequently reported in male subjects. These characteristics are more pronounced in athletes also due to a greater cardiovascular remodelling in male subject in response to exercise training. In addition, pregnancy is a particular setting for the occurrence of arrhythmias both for diagnosis and treatment. Supraventricular arrhythmias are frequently expressed, while ventricular events are rare. Notably, women with CHD represent a population at higher risk of severe arrhythmic complications. We need further investigations to better define the mechanisms underlying these gender-related differences: physical, autonomic and hormonal effects are certainly involved, but their role still needs to be fully characterized. More importantly, females are seldom represented in clinical research (i.e. one-fifth to one-fourth of the enrolled patients) and are infrequently referred for electrical treatments for arrhythmias and heart failure in clinical practice. Among the various explanations, a difference in epidemiology and in clinical response is far from being the most important.

Conflict of interest: none declared.

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