Cardiovascular Disease in Women (IV)

Cardiac Arrhythmias in Women

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The aim of this study was to review published data on gender differences in cardiac electrophysiology and in the presentation and clinical treatment of arrhythmias.

The evidence from studies published to date show that women have a higher mean resting heart rate, a longer QT interval, a shorter QRS duration, and a lower QRS voltage than men. Women have a higher prevalence of sick sinus syndrome, inappropriate sinus tachycardia, atrioventricular nodal reentry tachycardia, idiopathic right ventricular tachycardia, and arrhythmic events in the long-QT syndrome. In contrast, men have a higher prevalence of atrioventricular block, carotid sinus syndrome, atrial fibrillation, supraventricular tachycardia due to accessory pathways, Wolff-Parkinson-White syndrome, reentrant ventricular tachycardia, ventricular fibrillation and sudden death, and the Brugada syndrome.

With regard to implantable devices, it has been reported that defibrillators offer similar benefits in men and women. Moreover, there is no gender difference in the percentage who respond well to resynchronization therapy: survival is similar in the 2 sexes. However, it should be noted that few women have participated in studies of all types of therapy, including catheter ablation, resynchronization therapy, and the use of implantable defibrillators.

Key words: *Woman. Arrhythmia. Sudden death.*

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Arritmias cardiacas en la mujer

El objetivo de esta revisión fue analizar las diferencias electrofisiológicas entre sexos ya descritas, así como la presentación y el tratamiento clínico de las arritmias en las mujeres.

La evidencia, según los datos de los estudios publicados hasta el momento, nos muestra que las mujeres tienen una frecuencia cardiaca media superior, un intervalo QT más largo, una menor duración del complejo QRS, así como un menor voltaje de éste respecto a los varones. Asimismo, en las mujeres son más frecuentes la enfermedad del nódulo sinusal, la taquicardia sinusal inapropiada, la taquicardia supraventricular intranodal, la taquicardia ventricular idiopática del ventrículo derecho y el síndrome QT largo congénito y adquirido; en cambio, en los varones, la prevalencia de las siguientes arritmias es mayor: bloqueo auriculoventricular, hipersensibilidad del seno carotídeo, fibrilación auricular, taquicardia supraventricular con vía accesoria, síndrome de Wolff-Parkinson-White, taquicardia ventricular por reentrada, fibrilación ventricular y muerte súbita, así como síndrome de Brugada.

Respecto a los dispositivos, se observó que tanto los varones como las mujeres obtienen un beneficio similar con el marcapasos y el desfibrilador, y tampoco hubo diferencias en el porcentaje de buena respuesta a la resincronización entre ambos sexos, con una supervivencia similar; sin embargo, llama la atención la escasa participación femenina en los estudios de investigación de todas las técnicas terapéuticas, ya sea la ablación como la resincronización o el desfibrilador automático implantable.

Palabras clave: *Mujer. Arritmia. Muerte súbita.*

INTRODUCTION

Studies suggest that the incidences of various types of cardiac arrhythmia are different for women and men, although in many cases we still do not know why this should be. Two principle mechanisms have been proposed to explain these differences between the sexes differential: hormonal effects on the expression or function of ion channels or, conversely, differences

TABLE 1. **Underlying Mechanisms Responsible for Electrophysiological Differences Between Sexes**

Mecanism	Diferences
Electrophysiological cell effects	Presence of estrogen receptors
	Modulation of L-type Ca channels
	Modulation of K channels
Autonomic modulation	Physical condition
	Heart rate
	Heart rate variability
	Sensitivity of baroreceptors
	Dispersion of repolarization
	Expression of nitric oxide
Combinations of the above	Dispersion of repolarization
	Long QT syndrome

in autonomic tone. It is also possible that a combination of these 2 mechanisms may be involved (Table 1). A combined mechanism would lead to greater sympathetic activity and a lower baroreflex response in men of any age as well as to more pronounced parasympathetic or vagal activity in women.

Much of our information on the electrophysiological differences between the sexes is based on experimental animal models that used ovariectomized females treated with different gonadal steroids. The data from these studies suggest that the gonadal steroids are responsible for the differences, thanks to their effects on the ion channels of the cell membrane.

These differences between sexes have some clinical implications, particularly for the therapeutic approach and clinical treatment of arrhythmias in women.

In this article, we will review these electrophysiological differences and also the differences in presentation and clinical treatment of arrhythmias in women.

NORMAL ELECTROCARDIOGRAPHY AND ELECTROPHYSIOLOGY

Many electrocardiographic studies performed to date have reported differences between women and men in basal heart rate, heart rate variability, QT interval and duration, and QRS voltage.

Differences in Heart Rate

As long ago as 1920, Bazett[1] observed that women had a higher heart rate than men. This observation was confirmed in subsequent studies, such as the one conducted by Liu et al[2] in a population of 5116 patients. These authors found that the mean heart rate was between 3 and 5 beats/min higher in women. To avoid the influence of vagal and sympathetic tone, Burke et al[3] designed a study with double autonomic blockade by administering propanolol and atropin. The investigators found that the sinus cycle length was shorter in women, suggesting that differences exist independently of the neurovegetative balance. This difference in frequency of sinus node automaticity between sexes is maintained at all ages.[3]

Heart Rate Variability

Several studies in which the subjects underwent 24-hour ambulatory electrocardiographic monitoring with a Holter recorder have shown that women have a smaller low-frequency component and a smaller high-frequency to low-frequency ratio over the range of heart rate variability.[4,5] This finding can be explained by hormonal influences and the predominance of vagal tone, as indicated in the study by Huikuri et al.[6] These investigators administered estrogen replacement therapy to postmenopausal women, and found that this therapy increased baroreflex response and low- and high-frequency components within heart rate variability, suggesting a hormonal influence on the autonomic cardiac modulation. The differences in heart rate variability between the sexes tend to disappear with age.

QT Interval

Bazett reported that women had a longer QT interval than men in the electrocardiogram (ECG), despite having higher heart rates.[1] In basal conditions, the QT interval in women is about 10 ms to 20 ms longer than in men. This difference becomes more marked during menstruation, when an enhanced response to drugs has also been reported.[4]

According to Bazett,[1] this difference in QT interval duration remained after correction for heart rate, an observation that was later confirmed by other investigators, such as Stramba et al[7] and Merri et al.[8] The differences in the duration of the QT interval are mediated by the effect of female hormones on Ca and K channel function. Female hormones may also mediate the length of the QT interval through effects on the fast and persistent sodium current and sodium-calcium exchange.[5]

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.[9]

Voltage and Duration of the QRS Complex

In women, a shorter QRS complex and a smaller QRS voltage have been reported. Although these differences could, initially, be attributed to the smaller heart in women, they persist even after correcting for cardiac mass and body weight.[10] Likewise, these

differences persist in disease states such as ventricular hypertrophy. A lack of awareness of these differences between sexes when interpreting the ECG results in women can negatively affect the validity of diagnosis made. Similarly, failure to recognize differences in QRS duration and voltage can make electrocardiographic criteria for ventricular hypertrophy more specific but less sensitive in women.[10]

A shorter P wave duration and PR interval have also been reported in women.[5]

Changes in Repolarization and its Clinical Significance

Not only is the duration of repolarization different for women, the so-called nonspecific repolarization changes in the 12-lead electrocardiogram are much more frequent in women. According to a recent study of electrocardiographic data taken from 38 000 postmenopausal women who participated in the Women's Health Initiative,[11] these changes in repolarization are frequent and may be a predictor of cardiovascular risk in women who have passed the menopause. The authors found that a wide QRS/T angle, prolonged QRS duration, prolonged corrected QT interval, and the reduced heart rate variability are electrical parameters that may be predictors of cardiovascular mortality in postmenopausal women.[11]

In summary, the mean sinus rate or rhythm of sinus node automaticity is greater in women, the heart rate variability in the frequency domain has fewer low-frequency components, something strictly related to the predominance of the parasympathetic nervous system. The other electrophysiological observation that differentiates women from men is the QT and QTc interval duration, which determines the ventricular refractory period. This is also longer in women.

We do not know the physiological causes of these differences, but variations in the QT/HR ratio arising from the different T wave morphology, hormonal influences on the membrane ion channels, autonomic tone, or a combination of these factors may all play a role. Another important characteristic is that most of these differences in cardiac electrophysiology appear after puberty.[5,9] For example, during adolescence, a decrease in the QT interval is observed in male subjects when male hormones (androgenic hormones) increase. This decrease might point to a direct hormonal effect on the physiology of the channel membranes that are implicated in cardiac repolarization.[12]

Women show a higher intrinsic heart rate. This higher heart rate is observed both with and without autonomic block, and is associated with a shorter sinus cycle and lower heart rate variability during the day. It could therefore be attributed to a direct effect of female hormones on cardiac physiology, given that the difference starts to appear in adolescence.[9] Similarly, the duration of the QT and QTc interval becomes shorter in men after puberty.[12]

DIFFERENCIAL ARRHYTHMIC FINDINGS IN WOMEN

Supraventricular Tachycardias and the Wolff-Parkinson-White Syndrome

Inappropriate sinus tachycardia appears almost exclusively in women. It usually affects middle-aged women who are in some way connected to the health profession. The cause of this permanent enhancement in sinus node automaticity is not known.[12]

The variation in the incidence of paroxysmal supraventricular tachycardias according to sex and age has been evaluated in some epidemiological studies. For example, Rodríguez et al,[13] in a retrospective assessment of 623 patients referred for electrophysiological evaluation, found a predominance of atrioventricular (AV) nodal reentrant supraventricular tachycardia with a higher prevalence in women–2:1 compared to men.

However, this ratio was inverted for supraventricular tachycardia due to an AV nodal reentrant mechanism with an accessory pathway circuit, that is, it was 2:1 for men with respect to women.[13] In this same study, 50% of the patients presented the first episode of tachycardia when they were between 20 years and 30 years old, and almost 80% before they were 40 years old, regardless of the substrate studied. All these data agree with those reported for the Framingham study.[14] Another recent study has reported electrophysiological differences between sexes for arrhythmias with 2 nodal pathways-the slow refractory pathway periods are shorter in the short pathway and AV cycle block lengths and the tachycardia cycle lengths are also shorter in women.[15]

The incidence of Wolff-Parkinson-White syndrome is 1/3000 in the general population and more frequent in men, occurring at a ratio of 2:1, like AV nodal reentrant tachycardias via an accessory pathway.[13]

It should also be mentioned that the incidence of sudden death in the Wolff-Parkinson-White syndrome is small, and that it is a clinical problem associated mainly with men aged less than 30 years. Atrial fibrillation associated with this syndrome is also more frequent in men.[16,17]

Studies of the disease in a population under 35 years or in young athletes have found an accessory pathway in 10% to 30% of the cases, with a clear predominance in men.[18]

Maurer et al[19] investigated the prevalence of exercise-induced supraventricular tachycardias in a

population of healthy volunteers and, although they did not see a statistically significant difference between men and women (6.0% vs 6.3%), prevalence increased with age in men but not women. This suggests that the natural history of supraventricular paroxysmal tachycardias is such that the first episodes often appear early in life. The incidence of these episodes decreases with age, particularly in women.

Rosano et al[20] performed a study in premenopausal women and showed that the incidence of supraventricular tachycardias is greater in the phase of the menstrual cycle in when progesterone concentrations increase (luteal phase). The exact electrophysiological effects of progesterone are not known, but these observations suggest that the hormone may exercise a proarrhythmic effect. Such a proarrhythmic effect has also been described in pregnant women.[17,19,20]

Differences in outcomes and/or complications have not been reported for treatment of nodal reentrant tachycardias by radiofrequency catheter ablation.[4,14,17]

Ablation techniques have a reported success rate higher than 95% in both sexes. For AV nodal reentrant tachycardias via an accessory pathway, therapeutic outcomes also show no differences, and the success rate for catheter ablation is higher than 90% in both men and women. The rates of recurrence and complications of the ablation procedures also show no differences between sexes. However, it has been reported that a smaller proportion of women benefit from this procedure and that, when ablation is indicated, they have had a longer history of tachycardias and have taken a larger number of antiarrhythmic drugs.[21]

In short, inappropriate sinus tachycardia occurs almost exclusively in women. Supraventricular paroxysmal tachycardias arising from nodal reentry are more prevalent in women. The first episode appears before the subject is 40 years old a third of the cases and the incidence decreases with age. In men, accessory pathways are more common, and serious complications of these arrhythmias are also more frequent. The reasons for these different prevalences are not known.

Atrial Fibrillation

Atrial fibrillation is the most common supraventricular arrhythmia, affecting 0.4% of the population. Its incidence increases with age, and it is associated not only with increased morbidity and stroke, but also with higher all-cause mortality.[22-25]

According to the results of the Framingham study,[23] this arrhythmia is 1.5 times more frequent in men than women. Nevertheless, it is highly prevalent in both sexes and differences between sexes in the incidence tend to even out in subjects over 70 years old. Feinberg et al,[24] however, found an equal absolute number of cases of atrial fibrillation between women and men, probably because of the longer average lifetimes of the women in their study.

Women tend to present with longer-lasting episodes of atrial fibrillation, with a faster ventricular response and a higher incidence of cardioembolic complications. Other studies[22-26] did not find statistically significant differences. In men, atrial fibrillation is associated with a 5.4-fold increase in ischemic heart disease, whereas valve disease and heart failure are the cardiac diseases predominantly associated with this arrhythmia in women. The incidence of atrial fibrillation is also greater in men after cardiovascular surgery. When atrial fibrillation occurs in women, survival is shorter, and therefore the risk is higher than in men. In the Framingham study, the cohort of patients with atrial fibrillation had an odds ratio (OR) for death of 1.5 in men and of 1.9 in women after multivariate adjustment.[23] Some studies have shown a greater severity of embolic strokes in women, and so being a women is currently considered as an additional risk factor for thromboembolic events.[25]

As for treatment, no significant differences were found between sexes with regard to control of heart rate, prevention of thromboembolic complications, cardioversion, and maintenance of sinus rhythm, although antiarrhythmic agents should be administered to women with precaution because of their longer QT interval and consequent greater risk of proarrhythmia.[26]

Digoxin, the drug usually used to control ventricular rate in permanent atrial fibrillation seems to increase mortality in women.[7] This finding may however be related to the serum drug concentrations reached; normal levels of digoxin in blood would not be harmful to women, but concentrations above 1.2 ng/mL could be.[27]

Catheter ablation in atrial fibrillation is currently making headway among the therapeutic options for this arrhythmia. Table 2 shows the female populations included in some of the pioneering studies with this technique, though these populations are small, and more women should be recruited for such studies to determine whether indeed there are any differences in outcomes and complications between sexes.[28,30]

Ventricular Arrhythmias and Sudden Death

Differences in ventricular tachycardia and sudden death between the sexes were also reported in the Framingham study.[32] After a follow-up of 26 years, the incidence of sudden death increased with the age of the population, with a predominance in men in all age groups and an overall ratio in the incidence of approximately 3:1 compared to woman. This

difference was explained by the epidemiology of the heart disease (in women, it appears 10 years to 20 years later). However, the most common underlying heart disease was ischemic heart disease for both sexes. Sudden death was reported in 40% of the men and 34% of the women with coronary artery disease. The incidence of sudden death is low in subjects of both sexes under 45 years old. Above this age, the incidence doubles with each additional decade of life, starting 20 years later in women. As mentioned earlier, although coronary artery disease is the most common underlying cardiovascular disease, in women, sudden death with no history of this disease is more common, particularly in subjects under 65 years old-below this age, 90% of the cases of sudden death occur with no history of coronary artery disease.[32]

A history of myocardial infarction increases the risk of sudden death by 4 in men and by 3 in women. Ten years after the infarction, the risk of sudden death was 5.3% in women and 11.9% in men. Left ventricular dysfunction in conjunction with coronary artery disease significantly increased the risk of sudden death in both men and in women, and constitutes the most important predictor of death, either of any cause or sudden death. The presence of isolated coronary artery disease is predictive of a higher mortality in women regardless of ejection fraction, and the presence of dyskinesia leads to an additional 5-fold increase. The most common anatomical arterial lesion in young female smokers is plaque erosion, causing acute myocardial infarction and/or sudden death. In contrast, anatomical lesions in women over 60 years of age (postmenopausal) resemble those found in men and include lesions such as plaque rupture. This rupture is responsible for coronary thrombosis and associated clinical events such as unstable angina, acute myocardial infarction, or sudden death.[32]

In a recent analysis of survival in the VALIANT study, conducted in 14 703 patients with heart failure and ventricular dysfunction after myocardial infarction, revealed that 1067 cases of sudden death were reported during follow-up. Of these, 67% occurred in men and 33% in women.[33]

Another recent epidemiological study on sudden death performed in the United States indicates that men have 50% higher age-adjusted risk of sudden death than women.[34] The reason for these differences between the sexes is probably the difference in the incidence of ischemic heart disease.

Albert et al,[35] in a retrospective study of the survivors of cardiac arrest referred for electrophysiological study found ischemic heart disease was the underlying cause in 80% of the men and only 45% of the women.

Another study identified systolic blood pressure, smoking, intraventricular block, ST-T changes, family history of myocardial infarction in relations under 60 years old, body mass greater than 30, and diabetes as long-term predictors of sudden death in women.[36]

TABLE 2. **Female Participation in Pioneering Studies of Ablation in Atrial Fibrillation***

Type of FA / Autor and Reference	Year of Publication	Patients	Men/ Women
Paroxysmal/Haissaguerre et al[28]	1998	45	35/10
Paroxysmal/Hocini et al[29]	2005	90	71/19
Chronic/Haissaguerre et al[30]	2005	60	57/3
Chronic/Oral et al[31]	2006	146	129/17

*AF indicates atrial fibrillation.

Data from the Framingham Study[32] and the studies of Moss et al[37] and Dittrich et al[38] indicate that ventricular premature beats increase the risk in men but not women. It was also shown that there is a correlation in men between the frequency of postinfarction ventricular premature beats and fatal arrhythmic episodes, a correlation that was not present in women.

Differences between the sexes exist for inducibility of ventricular arrhythmias with programmed electrical stimulation in electrophysiological studies,[39,40] and it is easier to induce ventricular arrhythmias in men with postinfarction scarring (95%) than in women (72%). In women with no coronary artery disease, such arrhythmias can only be induced 19% of the time.

Implantable Cardioverters-Defibrillators

An important aspect of the treatment of malignant ventricular arrhythmias and the prevention of sudden death with implantable cardioverters-defibrillators is the difference in the number of devices placed in woman compared to men. None of the randomized controlled clinical trials done in primary or secondary prevention of sudden death recruited more than 32% of women in their study populations (Tables 3 and 4).[41-50] Explanations for this disparity include the lower incidence of sudden death in women, the lower rate of inducibility with programmed electrical stimulation, and the appearance of ischemic heart disease at older ages in women, which in turn might discourage placement of such a device. Added to these factors, there is the general tendency in clinical research to recruit fewer women.

A clinical study has confirmed that women with an implantable cardioverter-defibrillator are younger, have better left ventricular function, require assistance more for fibrillation than for ventricular tachycardia, and have less structural heart disease and experience fewer arrhythmic events than men.[51] This latter difference could be explained by a lower susceptibility

TABLA 3. **Female Participation in Randomized Studies in Primary Prevention of Sudden Death With Implantable Cardioverters-Defibrillators**

Study and Reference	Year of Publication	Patients, n	Women, %
MADIT[41]	1996	196	14
MADIT II[42]	2002	1232	16
CABG Patch[43]	1997	704	10
COMPANION[44]	2004	1520	32
DEFINITE[45]	2004	458	29
DINAMIT[46]	2004	674	24
SCD HeFT[47]	2004	2521	23.5

TABLE 4. **Female Participation in Randomized Studies in Secondary Prevention of Sudden Death With Cardioverters-Defibrillators**

Study and Reference	Year of Publication	Patients, n	Women, %
AVID[48]	1997	1016	20
CASH[49]	2000	288	20
CIDS[50]	2000	659	15.5

to ventricular arrhythmias in response to ischemia or stress. In controlled studies, however, the benefit of cardioverters-defibrillators has been shown to be similar in both men and women.[41,50] Zareba et al,[52] in a substudy of the MADIT II, monitored patients with a history of acute myocardial infarction who presented severe systolic dysfunction and who had received an implantable cardioverter-defibrillator. Of the 1232 patients included in the MADIT II, 192 (16%) were women and 1040 (84%) were men (Table 3). Comparison of the differences in this population according to sex showed that a higher percentage of women were NYHA functional class II or above (70% vs 63%; *P*=.067), hypertensive (60% vs 52%; *P*=.047), diabetic (42% vs 34%; *P*=.027), or had left-bundle-branch block (25% vs 17%; *P*=.011), whereas a lower percentage had a history of bypass surgery (42% vs 60%; *P*<.001). In the 2-year follow-up period, there were no significant differences between men and women for mortality in the patients randomized to receive conventional treatment (20% and 30%, respectively; *P*=.19). Likewise, no significant differences between sexes were found in the group assigned to cardioverter-defibrillator placement (women 16%, mean 16%; *P*=NS), the incidence of admission to hospital for heart failure (women 34%, men 24%; *P*=NS), or death or admission to hospital for heart failure (women 41%, men 31%; *P*=NS). The risk of appropriate implantable cardioverter-defibrillator therapy for VT/VF was smaller in women (OR=0.60; 95% confidence interval [CI], 0.37-0.98; *P*=.039). Therefore, in the MADIT II, mortality and therapeutic effectiveness of the implantable cardioverter-defibrillator was similar for both men and women, although women had a lower risk of suffering episodes of ventricular tachycardia.[52]

Other Ventricular Arrhythmias

Idiopathic right-ventricular tachycardia has 2 different phenotypes, one with repetitive, unsustained episodes of monomorphic ventricular tachycardia, and the other with sustained exercise-induced paroxysmal tachycardia. In both types, QRS morphology is a left-bundle-branch block configuration with an inferior axis and the arrhythmia is sensitive to adenosine. The mechanism is presumably related to the activity triggered by delayed postdepolarization in turn mediated by cyclic AMP. A higher prevalence has been reported in women.[53,54]

Idiopathic left-ventricular tachycardia or fascicular tachycardia on the other hand is more prevalent in men.[53,54]

Arrhythmogenic right-ventricular dysplasia is a condition characterized by replacement of muscle by fibrous or fibrofatty tissue. It is more frequent in young adults, with a ratio of incidence in men compared to women of 2.7:1. The estimated prevalence is 0.02%-0.1% in the general population. Dysplasia is assumed to be the cause of sudden death in young athletes in 5% of the autopsies done in the United States, and this percentage is as high as 25% in the autopsies done in northern Italy. A family history is reported in 50% of the cases, and several of the implicated genes have been identified.[55,56]

Congenital and Acquired Long QT Syndrome

The high incidence of arrhythmic events in women, and particularly ventricular tachycardia in *torsade de pointes*, has been described in association with long QT syndromes, whether congenital or acquired.[57-62]

The findings of the international registry on congenital long QT syndrome and studies with antiarrhythmic drugs in the production of proarrhythmic effects have provided some information on possible mechanisms. In the registry on congenital long QT syndrome, 58% of those included were women.[59] Male subjects were more likely to suffer syncope and sudden death of unknown cause up until puberty. Thereafter, the predisposition was greater in women.[59] Likewise, women with congenital long QT syndrome were at a higher risk of cardiac events in the period after giving birth. These events could be prevented with administration of beta-blockers.[57,60,61]

The Jervell-Lange-Nielsen syndrome, a variant of the congenital long QT syndrome associated with deafness, is a severe variant of the long QT syndrome caused by mutation of the genes that code for proteins

that modulate the current through the IKs channel. In these patients, men are at a higher risk of serious arrhythmic events.[62]

Makkar et al[63] reviewed 332 patients with drug-induced *torsade de pointes* and found that 70% were women, a percentage that was independent of left ventricular function, electrolytic imbalances, and the basal QT interval.

The SWORD study with sotalol was terminated prematurely because of increased mortality with the drug compared to placebo. A 4.7-fold increase in the risk of proarrhythmia and sudden death in women was shown. These results were later confirmed in subsequent studies also with sotalol in a number of patient populations.[64-66]

Table 5 shows the differences reported, according to sex, in the incidence of *torsade de pointes* induced by different drugs in a variety of studies.[63-69]

TABLE 5. **Differences Between Sexes in the Incidence of Drug-Induced *Torsades de Pointes***

Author, Year, and Reference	Drug	Women/Men, %
Makkar et al, 1993[63]	Various	70/30
Lehmann et al, 1996[64]	Sotalol	68/32
Woosley et al, 1993[67]	Terfenadine	60/40
Drici et al, 1998[68]	Erythromycin	70/30
Renoehl et al, 1996[69]	Probucol	94/6

Brugada Syndrome

Sudden death in patients with Brugada syndrome usually occurs during sleep, particularly in the early hours of the morning,[70] and when patients are in their 30s and 40s, although cases have been described in 1-year-old children and patients aged 77 years.

There is a higher prevalence in men, and this prevalence is very marked in certain regions, such as Southeast Asia, where the ratio of men to women with this syndrome is 8:1.[70]

ARRHYTHMIAS AND PREGNANCY

Some reports in the literature indicate that the incidence of both supraventricular arrhythmias[71] and ventricular ones[72,73] increases during pregnancy. However, the supporting evidence is limited and based on case studies. Likewise, the mechanisms for this increase are not clear. Possible proarrhythmogenic mechanisms include changes in autonomic tone, hemodynamic variations, and/or hormonal effects associated with pregnancy.

Given that clinical presentation of idiopathic supraventricular and ventricular arrhythmias is common in women of childbearing age, it is possible that there is no causal relationship between pregnancy and arrhythmias and that reports during pregnancy are merely a coincidence.

Treatments for rhythm disorders during pregnancy can be complicated by the additional risk of fetal damage. Prolonged and continuous treatments with antiarrhythmic drugs should be avoided, at least during the first 3 months of pregnancy. Low doses of beta-blockers are the safest option in pregnant women. However, cases have been described of low weights at birth, hypoglycemia, respiratory distress, and bradycardia, even with reasonably low doses of beta-blockers.

Digoxin, quinidine, and sotalol are also safe drugs and have been widely used. Amiodarone should be avoided because it is associated with hypoglycemia and miscarriages.[4,17]

Supraventricular tachycardias can be treated acutely with intravenous adenosine, whereas verapamil is contraindicated.

Electrophysiological studies, catheter ablation, and device placement should all be postponed until after birth because of the risk of fetal deformations associated with exposure to x-rays.

BRADYARRHYTHMIAS AND CARDIAC RESYNCHRONIZATION

Sick sinus syndrome is more frequent in women, whereas and AV block and carotid sinus syndrome are more common in men. Electrophysiological variations in sinus function have been described, with longer recovery times in men, and variations in AV conduction, with a longer AV block cycle length in men than in women[74] (Table 6).

The AV block cycle length is also longer and there is a greater incidence of lack of retrograde AV conduction (23% in men vs 11% in women).[74]

There are no differences between the sexes in need for pacemaker placement. However, some variations in outcomes have been reported. In one study, 6505 patients were implanted with a cardiac pacing device. Follow-up lasted 30 years and the primary outcome measure was all-cause mortality.[75] The mean survival was 101.9 months (8.5 years), with 44.8% of the patients alive after 10 years and 21.4% alive after 20 years. In all subgroups, women had a significantly longer survival than men (118 months vs 91.7 months; $P<.0001$). According to the analysis of survival at 5 years (men 61%, women 70%), at 10 years (men 40%, women 49%), at 15 years (men 26%, women 34%), and 20 years (men 16%, women 25%), the percentage survival was greater in women in all age groups. Likewise, women with sick sinus syndrome survived longer (145 months vs 115 months; $P=.02$). When complete AV block was present, longer survival was also observed in women than in men (106 months vs 83 months; $P<.0001$), with a similar finding in patients

TABLA 6. **Differences in the Incidence of Bradyarrhythmias and Tachyarrhythmias According to Sex***

	Predominance in Men	Predominance in Women
Bradyarrhythmia	AV block. Carotid sinus syndrome	SSS
Supraventricular tachyarrhythmia	Atrial premature beats. AF. SVT via accessory pathway WPW	IST INT.
Ventricular tachyarrhythmia	Ventricular premature beats. Reentrant VT. VF. Sudden death. Brugada syndrome	Idiopathic RV VT. Congenital ILQTS. Acquired LQTS

*SSS indicates sick sinus syndrome; AF, atrial fibrillation; LQTS, long QT syndrome; INT, intranodal tachycardia; IST, inappropriate sinus tachycardia; SVT, supraventricular tachycardia; VT, ventricular tachycardia; VF, ventricular fibrillation; WPW, Wolff-Parkinson-White; RV, right ventricular.

with atrial fibrillation (93 months in women, 70 months in men; *P*<.01).[75]

Bleeker et al[76] have recently analyzed possible differences in the response to cardiac resynchronization therapy among men and women. The study included 137 men and 36 women. There were no significant differences in the baseline characteristics, except that women had a higher percentage of nonischemic cardiomyopathy than men (women 67%, men 38%; *P*<.005). There were no differences in the improvement in NYHA functional class (women, 0.9 [0.6]; men, 1 [0.7]; *P*=NS) or in the increase in ejection fraction (women, 8% [8%]; men, 7% [9%]; *P*=NS). There were no differences between sexes for the percentage of those responding well to resynchronization (women, 76%; men, 80%; *P*=NS), and survival after 2 years of follow-up was similar (women, 84%; men, 80%; *P*=NS). Once again, the limited participation of women in clinical trials stands out, in this case in an investigation involving a novel therapy for heart failure.

REFERENCES

1. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart. 1920;7:353-70.
2. Liu K, Ballew C, Jacobs DR Jr, Sidney S, Savage PJ, Dyer A, et al. Ethnic differences in blood pressure, pulse rate, and related characteristics in young adults. The CARDIA study. Hypertension. 1989;14:218-26.
3. Burke JH, Goldberger JJ, Ehlert FA, Kruse JT, Parker MA, Kadish AH. Gender differences in heart rate before and after autonomic blockade: evidence against an intrinsic gender effect. Am J Med. 1996;100:537-43.
4. Villareal RP, Woodroof AL, Massumi A. Gender and cardiac arrhythmias. Tex Heart Inst J. 2001; 28:265-275.
5. James AF, Choosy SC, Hancox JC. Recent advances in understanding sex differences in cardiac repolarization. Prog Biophys Mol Biol. 2005. Disponible en: www.sciencedirect.com
6. Huikuri HV, Pikkujamsa SM, Airaksinen KE, Ikaheimo MJ, Rantala AO, Kauma H, et al. Sex-related differences in autonomic modulation of heart rate in middle-aged subjects. Circulation. 1996;94:122-5.
7. Stramba-Badiale M, Locati EH, Martinelli A, Courville J, Schwartz PJ. Gender and the relationship between ventricular repolarization and cardiac cycle length during 24-h Holter recordings. Eur Heart J. 1997;18:1000-6.
8. Merri M, Benhorin J, Alberti M, Locati E, Moss AJ. Electrocardiographic quantitation of ventricular repolarization. Circulation. 1989;80:1301-8.
9. Rautaharju PM, Zhou SH, Wong S, Calhoun HP, Berenson GS, Prineas R, et al. Sex differences in the evolution of the electrocardiographic QT interval with age. Can J Cardiol. 1992;8:690-5.
10. Okin PM, Roman MJ, Devereux RB, Kligfield P. Gender differences and the electrocardiogram in left ventricular hypertrophy. Hypertension. 1995;25:242-9.
11. Rautaharju P, Kooperberg C, Larson J, Lacroix A. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women. Circulation. 2006;113: 473-80.
12. Krahn AD, Yee R, Klein GJ, Morillo C. Inappropriate sinus tachycardia: evaluation and therapy. J Cardiovasc Electrophysiol. 1995;6:1124-8.
13. Rodriguez LM, de Chillou C, Schlapfer J, Metzger J, Baiyan X, van den Dool A, et al. Age at onset and gender of patients with different types of supraventricular tachycardias. Am J Cardiol. 1992;70:1213-5.
14. Benjamin EJ, Levy D, Vaziri SM, d'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994; 271:840-4.
15. Liuba I, Jonsson A, Safstrom K, Waldfridsson H. Gender related differences in patients with atrioventricular nodal reentry tachycardia. Am J Cardiol. 2006;97:384-8.
16. Pappone C, Vincenzo S. Catheter ablation should be performed in asymptomatic patients with Wolff-Parkinson-White syndrome. Circulation. 2005;112:2207-15.
17. Wolbrette D, Hemantkumar P. Arrhythmias and women. Curr Opinion Cardiol. 1999;14:36-48.
18. Puranik R, Chow CK, Duflou JA, Kilborn MJ, McGuire MA. Sudden death in the young. Heart Rhythm. 2005;2:1277-82.
19. Maurer MS, Shefrin ED, Fley TC. Prevalence and prognostic significance of exercise-induced supraventricular tachycardia in apparently healthy volunteers. Am J Cardiol. 1995;75:788-92.
20. Rosano GM, Panina G. Oestrogens and the heart. Therapie. 1999; 54:381-5.
21. Dagres N, Clague JR, Breithardt G, Borggrefe M. Significant gender-related differences in radiofrequency catheter ablation therapy. J Am Coll Cardiol. 2003;42:1103-7.
22. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults. National implications for rhythm management and stroke prevention: the AntiCoagulation and Risks Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285:2370-5.
23. Benjamin EJ, Wolf PA, d'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham heart study. Circulation. 1998;98:946-52.
24. Feinberg WM, Blackshear JL, Laupacis A, Kronmol R, Hart RG. Prevalence, age distribution and gender of patients with atrial fibrillation. Arch Intern Med. 1995;155:469-73.
25. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, et al. Gender differences in the risk of ischemic stroke and

peripheral emboli: in atrial fibrillation: the Anticoagulation and Risk factors in Atrial fibrillation (ATRIA) study. Circulation. 2005;112:1687-91.
26. Rienstra M, van Veldhuisen DJ, Hagens VE, Ranchor AV, Veeger NJ, Crijns HJ, et al. Gender related differences in rhythm control treatment in persistent fibrillation: data of the Rate Control versus Electrical Cardioversion. J Am Coll Cardiol. 2005;4: 1298-306.
27. Adams KF, Patterson JH, Gattis WA, O'Connor CM, Lee CR, Schwartz TA, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. J Am Coll Cardiol. 2005;46: 497-504.
28. Haissaguerre M, Jais P, Sha DC, Takahasi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339: 659-66.
29. Hocini M, Jais P, Sanders P, Takahasi A, Rotter M, Rostock Th, et al. Techniques, evaluation and consequences of linear block at the left atrial roof in paroxysmal atrial fibrillation. A prospective and randomized study. Circulation. 2005;112:3688-96.
30. Haissaguerre M, Sanders, Hocini M, Takahasi A, Rotter M, Sacher F, et al. Catheter ablation of long lasting persistent atrial fibrillation. J Cardiovasc Electrophysiol. 2005;16:1125-37.
31. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F, et al. Circumferential pulmonary vein ablation for chronic atrial fibrillation. N Engl J Med. 2006;354:934-41.
32. Kannel WB, Wilson PW, d'Agostino RB, Cobb J. Sudden coronary death in women. Am Heart J. 1998;136:205-12.
33. Solomon SD, Zelenkofske S, McMurray JV, Finn PV, Velazquez E, Ertl G, et al, for the VALIANT trial investigators. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure or both. N Engl J Med. 2005;352:2581-8.
34. Zheng Z, Croft JB, Giles WH, Mensha GA. Sudden cardiac death in the United states 1989 to 1998. Circulation. 2001;104:2158-63.
35. Albert CM, McGovern BA, Newell JB, Ruskin JN. Sex differences in cardiac arrest survivors. Circulation. 1996;93:1170-6.
36. Cupples LA, Gagnon DR, Kannel WB. Long- and short-term risk of sudden coronary death. Circulation. 1992;85: I11-8.
37. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, et al. The long QT syndrome. Prospective longitudinal study of 328 families. Circulation. 1991;84:1136-44.
38. Dittrich H, Gilpin E, Nicod P, Cali G, Henning H, Ross J Jr. Acute myocardial infarction in women: influence of gender on mortality and prognostic variables. Am J Cardiol. 1988;62:1-7.
39. Freedman RA, Swerdlow CD, Soderholm-Difatte V, Mason JW. Clinical predictors of arrhythmia inducibility in survivors of cardiac arrest: importance of gender and prior myocardial infarction. J Am Coll Cardiol. 1988;12:973-8.
40. Vaitkus PT, Kindwall KE, Miller JM, Marchlinski FE, Buxton AE, Josephson ME. Influence of gender on inducibility of ventricular arrhythmias in survivors of cardiac arrest with coronary artery disease. Am J Cardiol. 1991;67:537-9.
41. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary heart disease at high risk of ventricular arrhythmia. N Engl J Med. 1996;335:1933-40.
42. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber D, Cannom DS, et al. The multicenter automatic defibrillator implantation trial II investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346:877-83.
43. Bigger JT. Prophylactic use of implanted cardiac defibrillators in patients at high risk of ventricular arrhythmias after coronary artery graft surgery. CABG Patch trial investigators. N Engl J Med. 1997;337:1569-75.
44. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, de Marco T, et al. Comparison of medical therapy, pacing and defibrillation in advanced chronic heart failure COMPANION investigators. Cardiac resynchronization therapy with or without implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140-50.
45. Kadish A, Dyer A, Daubert J, Quigg R, Estes NA, Anderson K, et al. Defibrillators in non-ischemic cardiomyopathy treatment evaluation(DEFINITE) investigators. Prophylactic implantation in patients with non-ischemic dilated cardiomyopathy. N Engl J Med. 2004;350:2151-8.
46. Hohnloser SH, Kuck H, Dorian P, Roberts RS, Hampton JR, Hatala R, et al, the DINAMIT investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med. 2004;351:2481-8.
47. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. The sudden cardiac death in heart failure trial (SCD HeFT) investigators. Amiodarone or an implantable cardioverter defibrillator for congestive heart failure. N Engl J Med. 2005;352: 225-37.
48. The antiarrhythmics versus implantable defibrillator (AVID) investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997;337:1576-83.
49. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest. Circulation. 2000; 102:748-54.
50. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. The Canadian Implantable defibrillator study (CIDS): a randomised trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000;101:1297-302.
51. Lampert R, McPherson CA, Clancy JF, Caulin-Glaser TL, Rosenfeld LE, Bastford WP. Gender differences in ventricular arrhythmia recurrence in patients with coronary artery disease and implantable cardioverter defibrillator. J Am Coll Cardiol. 2004;43: 2239-99.
52. Zareba W, Moss AJ, Hall J, Wilber DJ, Ruskin JN, McNitt S, et al, for the MADIT-II investigators. Clinical course and implantable cardioverter defibrillator therapy in postinfarction women with severe left ventricular dysfunction. J Cardiovasc Electrophysiol. 2005;16:1265-70.
53. Nakagawa M, Takahashi N, Nobe S, Ichinose M, Ooie T, Yufu F, et al. Gender differences in various types of idiopathic ventricular tachycardia. J Cardiovasc Electrophysiol. 2002;13:633-8.
54. Lamberti F. Gender differences in idiopathic ventricular tachycardia. J Cardiovasc Electrophysiol. 2002;13:639-40.
55. Calkins H. Arrhythmogenic right ventricular dysplasia cardiomyopathy. Curr Opin Cardiol. 2006;21:55-63.
56. Kies P, Boersma M, Bax J, Schalij M, van der Wall E. Arrhythmogenic right ventricular dysplasia cardiomyopathy: screening, diagnosis and treatment. Heart Rhythm. 2006;3:225-34.
57. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, et al. The long QT syndrome. Prospective longitudinal study of 328 families. Circulation. 1991;84:1136-44.
58. Ebert SN, Liu XK, Woosley RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. J Women's Health. 1998;7:547-57.
59. Locati EH, Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Lehmann MH, et al. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: findings from the International LQTS Registry. Circulation. 1998; 97:2237-44.
60. Lehmann MH, Timothy KW, Frankovich D, Fromm BS, Keating M, Locati EH, et al. Age-gender influence on the rate-corrected QT interval and the QT-heart rate relation in families with genotypically characterized long QT syndrome. J Am Coll Cardiol. 1997;29:93-9.
61. Rashba EJ, Zareba W, Moss AJ, Hall WJ, Robinson J, Locati EH, et al. Influence of pregnancy on the risk for cardiac events in patients with hereditary long QT syndrome. LQTS Investigators. Circulation. 1998;97:451-6.
62. Schwartz PJ, Spazzolini C, Crotti L, Bathen J, Amilie JP, Timothy K, et al. The Jervell and Lange-Nielsen Syndrome. Circulation. 2006;113:783-90.

63. Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA. 1993; 270:2590-7.
64. Lehmann MH, Hardy S, Archibald D, Quart B, MacNeil DJ. Sex difference in risk of torsade de pointes with d,l-sotalol. Circulation. 1996;94:2535-41.
65. Pratt CM, Camm AJ, Cooper W, Friedman PL, MacNeil DJ, Moulton KM, et al. Mortality in the Survival With ORal D-sotalol (SWORD) trial: why did patients die? Am J Cardiol, 1998;81: 869-76.
66. Kuhlkamp V, Mermi J, Mewis C, Seipel L. Efficacy and proarrhythmia with the use of d,l-sotalol for sustained ventricular tachyarrhythmias. J Cardiovasc Pharmacol. 1997;29:373-81.
67. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. JAMA. 1993;269:1532-6.
68. Drici MD, Knollman BC, Wang WX, Woosley RL. Cardiac actions of erythromycin: influence of female sex. JAMA. 1998;280: 174-6.
69. Reinoehl J, Frankovich D, Machado C, Kawasaki R, Baga JJ, Pires LA, et al. Probucol associated tachyarrhythmic events and QT prolongation: importance of gender. Am Heart J. 1996;131: 1184-91.
70. Sarkozy A, Brugada P. Sudden cardiac death and inherited arrhythmia syndromes. J Cardiovasc Electrophysiol. 2005;16:S8-20.
71. Tawan M, Levine J, Mendelson M, Goldberger J, Dyer A, Kadish A. Effect of pregnancy on paroxysmal supraventricular tachycardia. Am J Cardiol. 1993;72:838-40.
72. Wilderhorn J, Wilderhorn A, Rahimtoola S, Elkayam U. WPW syndrome during pregnancy: increased incidence of supraventricular arrhythmias. Am Heart J.1992;123:769-98.
73. Brodsky M, Doria R, Allen B, Sato D, Thomas G, Sada M. New onset ventricular tachycardia during pregnancy. Am Heart J. 1992;123:933-41.
74. Liu S, Yuan S, Kongstad O, Olsson SB. Gender differences in the electrophysiological characteristics of atrioventricular conduction system and their clinical implications. Scand Cardiovasc J. 2001; 35:313-7.
75. Brunner M, Olschewski M, Geibel A, Bode C, Zehender M. Long term survival after pacemaker implantation. Eur Heart J. 2004;25: 88-95.
76. Bleeker GB, Schalij MJ, Boersma E, Steendijk P, van der Wall EE, Bax JJ. Does a gender difference in response to cardiac resynchronization therapy exists? Pacing Clin Electrophysiol. 2005;28:1272-5.