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.
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 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 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 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.

**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.

This finding can be explained by hormonal influences and the predominance of vagal tone, as indicated in the study by Huikuri et al. 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. 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. According to Bazett, 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 and Merri et al. 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.

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 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. Likewise, these differences in QRS voltage are independent of the neurovegetative balance. This difference in frequency of sinus node automaticity between sexes is maintained at all ages.

<table>
<thead>
<tr>
<th>Underlying Mechanisms Responsible for Electrophysiological Differences Between Sexes</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolytological cell effects Presence of estrogen receptors Modulation of L-type Ca channels Modulation of K channels</td>
<td></td>
</tr>
<tr>
<td>Autonomic modulation Heart rate Heart rate variability Sensitivity of baroreceptors</td>
<td></td>
</tr>
<tr>
<td>Dispersion of repolarization Expression of nitric oxide Dispersión of repolarization Long QT syndrome</td>
<td></td>
</tr>
<tr>
<td>Combinations of the above</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 1.
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.¹⁰

**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.¹⁹ 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.¹¹

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.⁷ Similarly, the duration of the QT and QTc interval becomes shorter in men after puberty.¹²

**DIFFERENTIAL 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.¹¹

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.¹¹ 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.¹¹ 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.²⁰

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.¹¹

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.¹¹,²⁰,²¹

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
Some studies have even suggested 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\(^7\) 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.\(^5,14,17\)

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 time. 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.
Female Participation in Pioneering Studies of Ablation in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Type of FA / Type of Ablation in Atrial Fibrillation</th>
<th>Year of Publication</th>
<th>Patients</th>
<th>Men/Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal/Haissaguerre et al*</td>
<td>1998</td>
<td>45</td>
<td>35/10</td>
</tr>
<tr>
<td>Paroxysmal/His et al**</td>
<td>2005</td>
<td>90</td>
<td>71/19</td>
</tr>
<tr>
<td>Chronic/Haissaguerre et al***</td>
<td>2005</td>
<td>60</td>
<td>57/3</td>
</tr>
<tr>
<td>Chronic/Ort et al**</td>
<td>2006</td>
<td>146</td>
<td>129/17</td>
</tr>
</tbody>
</table>

*AF indicates atrial fibrillation.

The incidence of sudden death is low in subjects of 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 was lower in women compared to men, regardless of age or the presence of other risk factors. This latter difference could be explained by a lower susceptibility to coronary thrombosis and associated clinical events such as unstable angina, acute myocardial infarction, or sudden death. 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. 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. The reason for these differences between the sexes is probably the difference in the number of devices placed in women 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). Explorations 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. This latter difference could be explained by a lower susceptibility...
Likewise, women with congenital long QT syndrome were at a higher risk of cardiac events in the MADIT II 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).

### 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.\(^{52,53}\)

Idiopathic left-ventricular tachycardia or fascicular tachycardia on the other hand is more prevalent in men.\(^{52,53}\)

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 23% 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.\(^{60,61}\)

### 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.\(^{52}\) Male subjects were more likely to suffer syncope and sudden death of unknown cause up until puberty. Thereafter, the predisposition was greater in women.\(^{52}\) 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.\(^{52,60,61}\)

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 al63 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.67-69

**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 8:1.71

**ARRHYTHMIAS AND PREGNANCY**

Some reports in the literature indicate that the incidence of both supraventricular arrhythmias72 and ventricular ones73,74 increases during pregnancy. However, the supporting evidence is limited and based on case studies. Likewise, the mechanisms for this increase are not clear. Possible proarrhythmic mechanisms include changes in autonomic tone, hemodynamic variations, and 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.

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

<table>
<thead>
<tr>
<th>Author, Year, and Reference</th>
<th>Drug</th>
<th>Women/Men, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makkar et al. 199344</td>
<td>Various</td>
<td>70/30</td>
</tr>
<tr>
<td>Lehmann et al. 198944</td>
<td>Sotalol</td>
<td>68/32</td>
</tr>
<tr>
<td>Woosley et al. 199344</td>
<td>Terfenadine</td>
<td>60/40</td>
</tr>
<tr>
<td>Driz et al. 199845</td>
<td>Erythromycin</td>
<td>70/30</td>
</tr>
<tr>
<td>Renzetti et al. 199646</td>
<td>Probucol</td>
<td>94/6</td>
</tr>
</tbody>
</table>

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.75

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 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 women76 (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).77

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.78 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...
with atrial fibrillation (93 months in women, 70 months in men; *P < 0.01). Bleecker et al also 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 < 0.005). 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, 79%; *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

25. Fung MC, Singer DE, Chang Y, Hylek EM, Huxley LE, Jessvald NG, et al. Gender differences in the risk of ischemic stroke and...
43. Bigger JT. Prophylactic use of implanted cardiac defibrillators in
patients at high risk of ventricular arrhythmias after coronary ar-

E, et al. The multicenter automatic defibrillator implantation trial II in-
vestigators. Prophylactic implantation of a defibrillator in patients
with coronary heart disease at high risk of ventricular

40. Kies P, Boersma M, Bax J, Schalij M, van der Wall E. Arrhyth-
mogenic right ventricular dysplasia cardiomyopathy: screening,

39. Freedman RA, Swedlow CD, Sodeick-Dufilante V, Mason JW.
Clinical predictors of arrhythmia inducibility in survivors of card-
aic arrest: importance of gender and prior myocardial infarction.

tea myocardial infarction in women: influence of gender on morta-


36. Lamberti F. Gender differences in idiopathic ventricular tachycar-


tients with severe left ventricular dysfunction. J Cardiovasc Electrophy-


31. Kannel WB, Wilson PW, Agostino RB, Cobb J. Sudden coro-

30. Haissaguerre M, Sanders, Hocini M, Takahasi A, Rotter M, Sa-
\n\n\n\n\n\n
27. Adams KF, Patterson JH, Gattis WA, O'Connor CM, Lee CR,
Mason JW, et al. Defibrillation in patients with myocardial infar-

26. Bieren W, Wilson PW, Agostino RB, Cobb J. Sudden coro-


table cardioverter defibrillator therapy in postinfarction women with severe left ventricular dysfunction. J Cardiovasc Electrophy-
