Gender differences in cardiac electrophysiology and arrhythmias. Part 1.

[1]RAMESH M. GOWDA, [2]SABRINA L. WILBUR, [1]PAUL SCHWEITZER
New York, USA

GOWDA RM, WILBUR SL, SCHWEITZER P. **Gender differences in cardiac electrophysiology and arrhythmias. Part 1.** Cardiol 2006;15(6):296–302

Gender differences in cardiac pathophysiology and electrocardiographic parameters have been suggested since the early 20th century. More recently this has expanded to include cardiac electrophysiology. The mechanisms responsible for the disparities are being elucidated. Contributing factors may include: differing amounts of sex and gonadal steroids, differences in autonomic tone, and gender specific hemodynamic variables. Women have a longer corrected QT interval and men have a lower intrinsic heart rate. Atrial fibrillation is more common in men. Atrial fibrillation in men is often associated with coronary artery disease and in women with valvular heart disease. With advancing age, the gender difference in the prevalence of atrial fibrillation disappears, and women tend to develop elevated risk of stroke and poorer survival than their male counterparts, especially in those over 75 years of age. Accessory pathways causing re-entry tachycardia are more prevalent in men, while in women atrioventricular nodal re-entry tachycardia predominates. Women are more likely to develop drug induced arrhythmias, especially polymorphic ventricular tachycardia. Women have an increased propensity to develop torsade de pointes during complete heart block and symptomatic long QT syndrome. Men have a higher incidence of sudden cardiac death. Female survivors of cardiac arrest are less likely to have underlying coronary artery disease and have a lower frequency of inducible ventricular tachycardia at electrophysiologic study. Antiarrhythmic drug and device therapy for sudden cardiac death are equally efficacious in men and women. Incidence of arrhythmias, new onset, paroxysms and exacerbations are increased during pregnancy. Understanding the potential mechanisms responsible for the gender differences may dramatically alter patient care and influence future research.

Key Words: Gender differences – QT interval – Arrhythmias – Sudden cardiac death – Arrhythmias in pregnancy

GOWDA RM, WILBUR SL, SCHWEITZER P. **Rozdiely srdcovej elektrofyziológie a arytmie u mužov a žien. 1. časť.** Cardiol 2006;15(6):296–302

Pohlavné rozdiely medzi patofyziologickými a elektrokardiografickými parametrami sú známe už od začiatkov 20. storočia. V ostatných rokoch sa tieto rozdiely rozšírili aj na elektrofyziológiu srdca. Medzi predpokladané patogenetické faktory, zodpovedné za rozdiely medzi mužmi a ženami, sú pohlavné hormóny a tonus vegetatívneho nervového systému. Ženy majú dlhšiu korigovanú hodnotu QT intervalu a muži nižší bazálny pulz. Predsieňová fibrilácia je častejsia u mužov ako u žien. U mužov sa táto arytmia častejšie spája s ischemickou chorobou srdca a u žien s chlopňovými chybami. So starnutím pohlavné diferencie vo výskyte predsieňovej fibrilácie vymiznú. Okrem toho ženy nad 75 rokov majú väčšiu tendenciu k tromboembolickym príhodám a vyššiu mortalitu ako muži. Supraventrikulárne tachykardie u pacientov s preexcitáciou sú častejšie u mužov, kým átriokomorové nodálne tachykardie u žien. U žien je vyšší výskyt arytmií, vyvolaných liekmi, polymorfných komorových tachykardií, ako aj vyššia náchylnosť k „torsade de pointes" počas kompletného átrioventrikulárneho bloku a k predĺženému QT syndrómu. Incidencia náhlej srdcovej smrti je vyššia u mužov. Ženy, ktoré prežijú srdcovú zástavu, majú nižšiu pravdepodobnosť vzniku koronárnej choroby. „Inducibility" komorových tachykardií počas elektrofyziologického testovania je nižšia u žien ako u mužov. Antiaritmiká a defibrilátory sú rovnako účinné u mužov, ako aj u žien. Výskyt arytmií, nástup nového ochorenia, paroxyzmy a zhoršenie stavu sa zvyšuje počas tehotenstva. Porozumenie potenciálnych mechanizmov zodpovedných za pohlavné rozdiely môže v budúcnosti podstatne zmeniť starostlivosť o týchto pacientov a ovplyvniť budúci výskum.

Kľúčové slová: pohlavné rozdiely – QT interval – arytmie – náhla srdcová smrť – arytmie v tehotenstve

Introduction

Various clinical trials, literature reviews, epidemiological studies and outcomes data have identified sex differences in the incidence of various cardiac arrhythmias (1 – 4). These studies have also shown that gender differences may be an independent risk factor for certain arrhythmias. This review summarizes the published data with regard to sex differences in the occurrence and manifestations of various arrhythmias, including the effects of pregnancy and menstruation. Additionally we will review the available data at the electrophysiologic level that may help explain the above differences. Finally, we will discuss the implications which both the epidemiologic and the clinical data have for the future.

Heart rate

Gender differences on surface electrocardiograms have been known for over 8 decades (5, 6). Bazett's first description of a method for correcting the QT interval showed that a woman, on average, has a faster heart rate (5). Several large scale studies subsequently confirmed the results

From [1]Divisions of Cardiology, Beth Israel Medical Center, New York, NY and [2]Long Island College Hospital, Brooklyn, NY, USA
Manuscript received April 8, 2005; accepted for publication August 10, 2006
Address for correspondence: Paul Schweitzer, MD, FACC, Beth Israel Medical Center, 5 Baird, 17th Street 1st Avenue, New York, NY 10003, USA, email: pschweit@chpnet.org

of earlier small studies. One proposed explanation may be related to differences in physical conditioning and exercise capacity (1). In addition, both autonomic and non-autonomic factors may influence the sinus node. On the contrary, Jose et al. (7) hypothesized that the difference in heart rate after autonomic blockade is not gender related, but instead due to the intrinsic properties of the sinus node. Burke et al. (8) studied a group of men and women at maximal bicycle exercise. Men had a longer sinus cycle length (slower heart rate) than their female counterparts before and after autonomic blockade. However, covariate analysis showed the only significant predictor of sinus cycle length was maximum exercise capacity, not sex. Differences in heart rate variability patterns between normal men and women have also been studied (9). Tsuji et al. (10) studied clinical determinants of heart rate variability. Minor differences in one or more heart rate variability measures were observed in females. The true mechanism for sex differences in heart rate remains to be defined.

QRS, T wave & QT interval

There are sex differences in the amplitude of the QRS complex and the area under the T wave. Adolescents, in particular, demonstrate QRS complex amplitude that is larger in men when compared to women, especially pronounced in the precordial leads (11). A similar difference is also noted in the adult population (12). The significantly larger mean amplitude of the QRS complex in men is most impressively seen in leads V3 to V6 (11). It seems that sex differences in the amplitude of ventricular polarization reflected on the surface electrocardiogram are secondary to differences in left ventricular mass.

QT interval duration measures longer in women than men (6, 13, 14). The first description of longer corrected QT interval in women was by Bazett in 1920, which showed a mean difference of 24 milliseconds between men and women (5). Several studies using various methods of correcting the QT interval have confirmed this finding (12, 15); the most likely explanation being sex hormones having a direct and/or indirect effect on cardiac depolarization and repolarization, since the difference is not observed before puberty (16, 17). Estrogens facilitate bradycardia-induced prolongation of the QT interval and the emergence of arrhythmias, whereas androgens shorten the QT interval and blunt the QT response to drugs. The male corrected QT interval shortens at puberty and remains short until about 50 years of age; a period coinciding with the highest androgen levels. In an attempt to determine if the QT shortening was secondary to a lack of estrogen or a preponderance of testosterone, Bidoggia et al., (18) studied a group of castrated men and virilized women. The electrocardiographic patterns of repolarization in the castrated men were slower and longer than that of normal men. Women with virilization exhibited faster and shorter repolarization than normal women and castrated men. These differences are the opposite of those found in the normal population. The abnormal repolarization observed in castrated men normalized with the administration of testosterone, implying that testosterone plays an important role in modulating cardiac repolarization. Burke et al., (19) showed that the differences in autonomic tone and menstrual cycle variability in the corrected QT in women at rest do not appear to be responsible for the gender differences in the QT interval (19).

The gender differences in the corrected QT interval may be, to some extent, dependent on the correction formula used. A linear correction formula provides less of a sex difference than does the Bazett formula (11). Electrocardiographic studies have also shown a gender difference in QT/RR relationship, QT slope and in the dynamics of T wave generation. These differences, coupled with a longer baseline QT interval in women may help explain their higher incidence of torsade de pointes (13, 20). The female preponderance of QT prolongation is particularly relevant as we are learning more about the risk of sudden cardiac death associated with congenital and acquired long QT syndrome.

QT interval dispersion, when increased, is a proposed electrocardiographic marker of susceptibility to ventricular arrhythmias and of cardiovascular mortality. When principal component analysis of the T-wave vector loop ratios was used to quantify repolarization abnormalities among 1839 American Indians, an increased QT dispersion was found to be a significant predictor of cardiovascular mortality in women but not in men (21).

According to the population-based Rotterdam Study (22), a prolonged corrected QT interval was found to be an independent predictor for cardiac and all-cause mortality in older men and women. In women more than men an increased risk of cardiac death was associated with prolonged QT (22). These risk estimates did not change after adjustment for potential confounders, including a history of myocardial infarction, hypertension, and diabetes mellitus. In addition, the prolonged QT was hardly affected by the heart rate correction formula used (22).

Electrophysiologic testing

Kadish et al. (23) examined the cardiac electrophysiological gender differences in 100 consecutive patients,

without structural heart disease with similar indications for electrophysiological testing (EP). Men were found to have a longer sinus node recovery time after correction to baseline sinus rate.

There appear to be conflicting data regarding atrioventricular (AV) nodal and His-Purkinje conduction properties in men and women. In the data from Kadish et al. (23), AV nodal function, as measured by PR interval, AH interval, and AV Wenckebach cycle length, was similar in men and women. HV intervals in patients without pre-excitation and ventricular effective refractory periods were also similar in men and women (23). A caveat to this analysis was a small possibility of sex differences in right ventricular apical effective refractory period. On the contrary, Liu et al., (24) found that the PR interval, AH and HV intervals in men were significantly longer than in women. The AV node effective refractory period in men was longer than in women. However no significant sex differences were observed with respect to the incidence of AV nodal dual pathway physiology and the maximum AH interval achieved during premature stimulation or incremental pacing. AV- and ventriculoatrial block cycle length were found to be longer in men than in women. Men were twice likely to have ventriculoatrial dissociation during ventricular pacing than women (24).

Clinical arrhythmias

There are significant gender differences in the incidence of many clinical arrhythmias (**Table 1** and **2**). Part of this disparity may be attributed to known differences in the frequency of underlying structural heart disease. Women have smaller cardiac chamber size and smaller coronary artery diameter than men. The incidence of atrial fibrillation is higher in men than women and a few small reports also suggest a male predominance of atrial flutter. On the contrary, AV nodal reentrant tachycardia (AVNRT) appears to be more common in women than men, and is not dependent on underlying heart disease. Isolated premature beats in the absence of structural heart disease may not exhibit a sex predominance, but are often more symptomatic in women with mitral valve prolapse. The relative sex prevalence of uncommon arrhythmias such as atrial tachycardia, junctional tachycardia, and ventricular tachycardia, in the absence of structural heart disease is more difficult to determine due to only a small series of patients being reported.

Table 1 Gender differences of ECG changes and common arrhythmias

Female predominance	Male predominance
Higher baseline heart rate	Earlier CAD and associated VA
Longer QTc interval	Premature ventricular beats
Drug pro-arrhythmia (TDP)	Atrial fibrillation
Symptoms and sudden death in LQTS	Atrial flutter
Paroxysmal atrial tachycardia	W-P-W syndrome
AV nodal reentrant tachycardia	AV reentrant tachycardia
	Ventricular tachycardia
	Sudden cardiac death
	Ventricular fibrillation and cardiac arrest

AV – Atrioventricular, CAD – Coronary artery disease, VA – Ventricular arrhythmia

Supraventricular tachyarrhythmias and pre-excitation

The underlying mechanisms of the sex differences in supraventricular tachyarrhythmias (SVTs) are not clear. In one study of patients undergoing electrophysiologic testing, atrial tachycardia occurred in similar proportions in male and female subjects (4). Atrioventricular nodal reentrant tachycardia (AVNRT) has an increased female to male predominance. Accessory pathways, including Wolff-Parkinson-White (WPW) syndrome, occur more frequently in males (4, 25, 26). Furthermore, atrial and ventricular fibrillation occurs more often in male than female patients (4, 25). Also, men with WPW syndrome are more likely to experience atrial and ventricular fibrillation (27). Although patients symptomatic from an accessory pathway were more commonly male, orthodromic atrioventricular re-entrant tachycardia (AVRT) occurs more often in female than in male patients. Differences in the AV conduction properties might explain the above gender differences (24).

Symptoms of paroxysmal SVT may simulate panic disorder. Prior to eventual correct diagnosis, women are more likely than men to have their symptoms attributed to panic, anxiety, or stress, thus delaying the diagnosis of SVT (26). This observation might be of concern and analogous to the sex bias observed with respect to physician interpretation of symptoms in patients with coronary artery disease (28). Misdiagnosis or delayed diagnosis could result in the administration of inappropriate therapies. Documentation of the heart rhythm during symptoms with event monitors may be crucial in distinguishing an arrhythmia from a panic disorder.

Despite the differences in incidence of SVTs, there is no gender difference in success rates and outcomes among candidates who undergo radiofrequency (RF) catheter ablation (29, 30). However, a recent study reported significant gender-related referral and treatment differences among a large series of patients undergoing radiofrequency ablation of accessory pathways and AVNRT (30).

Table 2 Anti-arrhythmic agents and pregnancy

Drug	Indication	Potential adverse effect	FDA rating
Quinidine	Maternal and fetal SVT, VT, maternal malaria	Maternal and fetal thrombocytopenia, eight cranial nerve toxicity, Torsade de Pointes	C
Procainamide	Acute management of undiagnosed wide complex tachycardia	Lupus-like syndrome with chronic use, Torsade de Pointes	C
Disopyramide	Labor induction	Induction of uterine contractions, Torsade de Pointes	C
Lidocaine	Maternal VT, VF, arrhythmias due to digoxin toxicity	CNS adverse effects, bradycardia, fetal hypoglycemia	B
Mexiletine	VT	CNS adverse effects, fetal bradycardia, fetal hypoglycemia	C
Tocainide	VT	Dizziness, nausea	C
Phenytoin	Arrhythmias due to digoxintoxicity	Mental and growth retardation, fetal hydantoin syndrome	D
Flecainide,Propafenone	Maternal and fetal SVT, selected VTs	Increased mortality in patients with previous myocardial infarction, mild b-blocker effects (propafenone)	C
Beta antagonists	Maternal and fetal SVT, idiopathic VT, rate control in AF, maternal HTN, HCM, thyrotoxicosis	Intrauterine growth retardation, fetal bradycardia, fetal apnea, rarely hypoglycemia, hyperbilirubinemia, hypocalcemia, premature labor	C/D
Amiodarone	Maternal and fetal SVT, VT, VF	Maternal and/or fetal hypo- or hyperthyroidism, prematurity, fetal bradycardia, fetal QT prolongation, low birth weight, congenital malformations, spontaneous abortions	D
Sotalol	Maternal VT	Torsade de Pointes, bradycardia	B
Ibutilide	Pharmacological cardioversion of AF/Flutter	Torsade de Pointes	C
Verapamil, Diltiazem	Maternal and fetal SVT, idiopathic VT (verapamil), AF rate control, maternal HTN, premature labor (verapamil)	Maternal/fetal hypotension, fetal bradycardia and heart block, maternal hepatitis, depression of cardiac contractility, distal digital defects in fetus	C
Adenosine	Symptomatic narrow complex tachycardia	Transient fetal bradycardia	C
Digoxin	Fetal and maternal SVT, rate control in AF, HF	Premature labor, low birth weight	C

SVT – Supraventricular tachycardia, VT – Ventricular tachycardia, VF – Ventricular fibrillation, CNS – Central nervous system, AF – Atrial fibrillation, HTN – Hypertension, HCM – Hypertrophic cardiomyopathy, HF – Heart failure

United States Food and Drug Administration (FDA) ratings for drugs used in pregnancy are categorized into A, B, C and D. A. Well-controlled studies showed no risk to fetus; B. No evidence of risk to humans; C. Risk cannot be ruled out; D. Evidence of risk; X. Contraindicated in pregnancy.

There was a trend towards a more conservative approach in female patients, with delayed referral for ablation, after prolonged symptom duration, and after receiving more antiarrhythmic drugs compared to male patients. The procedural success, complications and recurrences after ablation procedures were similar in male and female patients. Potential concerns about the consequences of radiation exposure, especially with young patients in their reproductive years, might partly explain the referral bias. In addition to safety concerns, other potential reasons for the differences may include women better tolerating a similar degree of incapacitation than men, and a female tendency to marginalize their health issues and focus more on the wellbeing of the children/family (30).

Arrhythmias and menstrual cycle

There is a cyclical variation in the occurrence of episodes of arrhythmia with regards to the menstrual cycle. Both estrogen and progesterone have been implicated in effecting electrophysiologic parameters. A relationship exists between ovarian hormones and paroxysmal SVT (31 – 33). Perimenstrual associations may be more important for women who have AVNRT than those with AVRT due to accessory pathways. Rosano et al., (32) found a premenstrual clustering of spontaneous arrhythmias in a group of premenopausal women with SVT who underwent 48-hour ambulatory ECG recordings and determination of plasma concentrations of estradiol and progesterone. An increase in the number and duration of episodes of SVT was observed on day 28 as compared to day 7 of the menstrual cycle. Additional findings were a significant positive correlation for levels of progesterone and an inverse correlation for estradiol with respect to the number of episodes and duration of SVT. Thus it appears that high progesterone levels may be proarrhythmic, rather than high estrogen levels being antiarrhythmic.

Lown class 2 or greater ventricular arrhythmias are more frequent during the luteal phase (34). The presumed mechanism may be due to effects of ovarian hormones or to increased sympathetic activity occurring in the luteal phase of menstruation. For women with a history of perimenstrual clustering of SVT and those receiving estrogen replacement therapy, elective EP testing can be preferably scheduled at times of low estrogen levels (premenstrual or off estrogen replacement) to facilitate the probability of successful procedure (33). More studies are needed to know whether women without a history of perimenstrual clustering of symptoms might have had differential inducibility at midcycle versus perimenstrually.

Tse et al., (35) demonstrated a significant gender difference in atrial electrophysiologic changes in response to rapid atrial pacing and an increase in atrial pressure. During sinus rhythm, the mean atrial effective refractory period in premenopausal women was shorter than in postmenopausal women and age-matched men. Atrial effective refractory periods in all patients shortened significantly during atrial and simultaneous AV pacing. However, the degree of shortening during atrial pacing and during simultaneous AV pacing was significantly less in premenopausal women than in postmenopausal women or age-matched men. The effects of menopause on the observed changes suggest that the gender differences may be mediated by the effects of estrogen on atrial electrophysiologic properties (35). This it appears that both estrogen and progesterone play active roles in arrhythmia mechanisms.

Atrial fibrillation and atrial flutter

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population, with a higher male prevalence. The reason for the gender difference is unclear (36 – 39). Suttorp et al. (37) examined patients with paroxysmal AF or atrial flutter post-cardioversion and identified female gender as an independent predictor for recurrent or frequent episodes of arrhythmia. Female gender was also associated with an increased risk of a poor clinical course, irrespective of the therapeutic approach employed.

In the Framingham Study, no excess risk was found in women for the development of chronic AF (40). After adjusting for risk factors including age, men had a 1.5 times greater risk of developing AF than women (38). Although initially the incidence of AF is greater in men than in women, with advancing age the absolute numbers tend to equalize (41, 42). Feinberg et al. (41) found that 53% of all patients with AF were women. This is most likely attributable to the greater life expectancy of women over men, accompanied by the higher prevalence of AF with increasing age. In a contradictory study among the Japanese rural population, consisting of men and women aged 40 – 69 years, the age adjusted prevalence rates of AF showed no significant gender differences (43). Cameron et al., (39) analyzed the data on 18,343 patients with angiographically demonstrated coronary artery disease in the Coronary Artery Surgery Study (CASS) registry and AF was found to be present in 116 (0.6%) patients. Men had a 5.4 times increased risk of developing AF. The presence of AF was positively associated with the following clinical and angiographic variables: older age, sex (male), mitral regurgitation and functional impairment due to congestive heart failure. The number of diseased coronary arteries was negatively related to the presence of AF. Atrial fibrillation was an independent predictor of survival with its presence doubling the estimated risk over those patients without AF.

With regard to mean age, incidence of hypertension, smoking, diabetes mellitus, and left ventricular hypertrophy as noted on electrocardiogram (38, 40), the Framingham Heart Study cohort revealed trends in men and women with AF similar to the CASS registry. However, in men the AF was more likely to be related to myocardial infarction, and in women it was more commonly associated with congestive heart failure and valvular heart disease (38, 40, 42). In addition, advanced age and male gender are strong independent predictors of post-cardiac surgery AF (44 – 46).

The factors accounting for gender differences in risk and prognosis for patients with AF are not clear. Possible explanations are derived from differences noted in the expression of estrogen-mediated regulation of L-type calcium channels, hormonal effects on autonomic tone, three-dimensional myocardial architecture or disorientation, and differences in electrophysiology (1, 45, 47). These hypotheses are supported by the observations that a hyperadrenergic state may be a trigger for post cardiac surgery AF (46).

Significant gender differences in the therapy and outcome of patients with AF have been noted. The duration of paroxysmal AF episodes tend to be longer and the heart rate higher in females compared to males (2). Compared to men, women may be at increased risk for embolism and have increased mortality long-term (42, 48). Analysis of the Framingham Heart Study cohort revealed greater odds ratio for death among women with AF compared to men, diminishing the survival advantage of women (38). Gender is an important feature affecting the selection of antiarrhythmic therapy for AF, as women are more likely to develop drug-induced arrhythmias, complicating optimal management (42). Extra caution is required prior to choosing QT prolonging drugs in women (42).

The paroxysmal form of AF has the greatest impairment in quality of life with increased impact on women (2, 49). Personality attributes may have a role in influencing quality of life outcomes (49). In the Canadian Trial of Atrial Fibrillation (49) women reported worse physical health and functional capacity, but not mental health or general wellbeing. Women also had more frequent and severe cardiac symptoms than men. Physical health im-

proved significantly from baseline to 3 months among women and mental health improved among men. Cardiac symptom frequency and severity improved over time for both sexes. Tendency to somatize predicted poor quality of life, with women having higher scores than men. However, after controlling for somatization, women still had worse physical function, functional capacity, and symptom burden than men. Independent of cardiac disease severity and age, women with AF had significantly more impaired quality of life than men, specifically in domains related to physical rather than emotional functioning (49).

In summary, as discussed, there are important gender differences between men and women not only in the heart rate, but also in the amplitude of the QRS complexes and the duration of the QT interval. Furthermore there is some controversy whether women have longer PR, AH and HV intervals. In regard to various arrhythmias, there are not only differences in their incidence but also in their outcome and management. This is particularly true in patients with atrial fibrillation. Of interest is also the frequency of various atrial and ventricular arrhythmias varies during different phases of the menstruation cycle.

References

1. Larsen JA, Kadish AH. Effects of gender on cardiac arrhythmias. J Cardiovasc Electrophysiol 1998;9:655–664.
2. Hnatkova K, Walstare JEP, Murgatroyd FD. Age and gender influences on rate and duration of paroxysmal atrial fibrillation. PACE 1998;21:2455–2458.
3. Albert CM, McGovern BA, Newell JB, et al. Sex differences in cardiac arrest survivors. Circulation 1996;93:1170–1176.
4. Rodriguez LM, deChillou C, Schlapfer J, et al. Age at onset and gender of patients with different types of Supraventricular tachycardias. Am J Cardiol 1992;70:1213–1215.
5. Bazett H. An analysis of the time relations of electrocardiograms. Heart 1920;7:353–370.
6. Ashman R. The normal duration of the QT interval. Am Heart J 1942;23:522–534.
7. Jose A, Collison D. The normal range and determinants of the intrinsic heart rate in man. Cardiovasc Res 1970;4:160–167.
8. Burke J, Goldberger J, Ehlert FA, et al. Gender differences in heart rate before and after autonomic blockade: Evidence against an intrinsic gender effect. Am J Med 1996;100:537–543.
9. Ryan SM, Goldberger AL, Pincus SM, et al. Gender- and age-related differences in heart rate dynamics: are women more complex than men? J Am Coll Cardiol 1994;24:1700–1707.
10. Tsuji H, Venditti FJ Jr, Manders ES, et al. Determinants of heart rate variability. J Am Coll Cardiol 1996;28:1539–1546.
11. Macfarlane P, Lawrie T. Comprehensive electrocardiography. Theory and practice in health and disease. New York: Pergamon Press 1989:798.
12. Merri M, Benhorin J, Alberti M, et al. Electrocardiographic quantitation of ventricular repolarization. Circulation 1989; 80:1301–1308.
13. Stramba-Badiale M, Locati EH, Martinelli A, et al. Gender and the relationship between ventricular repolarization and cardiac cycle length during 24-h holter recordings. Eur Heart J 1997;18:1000–1006.
14. Molnar J, Zhang F, Weiss J, et al. Diurnal pattern of QTc interval: How long is it prolonged? Possible relation to circadian triggers of cardiovascular events. J Am Coll Cardiol 1996;27:76–83.
15. Goldberg RJ, Bengston Z, Chen Z, et al. Duration of QT interval and total and cardiovascular mortality in healthy persons (The Framingham Heart Study experience). Am J Cardiol 1991;67:55–58.
16. Rautaharju PM, Zhou SH, Wong S, et al. Sex differences in the evolution of the electrocardiographic QT interval with age. Can J Cardiol 1992;8:690–695.
17. Pham TV, Rosen MR. Sex, hormones, and repolarization. Cardiovasc Res 2002;53:740–751.
18. Bidoggia H, Maciel JP, Capalozza N, et al. Sex differences on the electrocardiographic pattern of cardiac repoloarization: possible role of testosterone. Am Heart J 2000;140:678–683.
19. Burke JH, Ehlert FA, Kruse JT, et al. Gender-specific differences in the QT interval and the effect of autonomic tone and menstrual cycle in healthy adults. Am J Cardiol 1997;79:178–181.
20. Yang H, Elko P, Fromm BS, et al. Maximal ascending and descending slopes of the T wave in men and women. J Electrocardiol 1997;30:267–276.
21. Okin PM, Devereux RB, Fabsitz RR, et al. Principal component analysis of the T wave and prediction of cardiovascular mortality in American Indians: the strong Heart Study. Circulation 2002;105:714–719.
22. de Bruyne MC, Hoes AW, Kors JA, et al. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. Eur Heart J 1999;20:278–284.
23. Kadish AH. The effects of gender on cardiac electrophysiology and arrhythmias. In: Zipes DP, Jalife J. Cardiac electrophysiology. From Cell to Bedside. Philadelphia: WB Saunders 1995:1268–1275.
24. Liu S, Yuan S, Kongstad O, et al. Gender differences in the electrophysiological characteristics of atrioventricular conduction system and their clinical implications. Scand Cardiovasc J 2001;35:313–317.
25. Wellens HJJ, Bar FW, Farre J, et al. Diagnosis and incidence of concealed accessory pathways in patients suffering from paroxysmal AV junctional tachycardias. Rev Lat Cardiol 1980;1:60–67.
26. Lessmeir TJ, Gamperling D, Johnson-Liddon V, et al. Unrecognized paroxysmal supraventricular tachycardia. Arch Intern Med 1997;157:537–543.
27. Torner Montoya P, Brugada P, Smeets J, et al. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. Eur Heart J 1991;12:144–150.
28. Ayanian JZ, Epstein AM. Differences in the use of procedures between women and men hospitalized for coronary artery disease. N Engl J Med 1991;325:221–225.

29. Calkins H, Yong P, Miller JM, et al. Catheter ablation of accessory pathways, atrioventricular nodal reentrant tachycardia and the atrioventricular junction. Circulation 1999;99:262–270.

30. Dagres N, Clague JR, Breithardt G, et al. Significant gender-related differences in radiofrequency catheter ablation therapy. J Am Coll Cardiol 2003;42:1103–1107.

32. Rosano GMC, Leonardo F, Sarrel PM, et al. Cyclical variation in paroxysmal supraventricular tachycardia in women. Lancet 1996;347:786–788.

33. Myerburg RJ, Cox MM, Interian A. Jr, et al. Cycling of inducibility of paroxysmal supraventricular tachycardia in women and its implications for timing of electrophysiologic procedures. Am J Cardiol 1999;83:1049–1054.

34. Lown B, Wolf M. Approaches to sudden death from coronary artery disease. Circulation 1971;44:130–142.

35. Tse HF, Oral H, Pelosi F, et al. Effect of gender on atrial electrophysiologic changes induced by rapid atrial pacing and elevation of atrial pressure. J Cardiovasc Electrophysiol 2001;12:986–989.

36. Selzer A. Atrial fibrillation revisited. N Engl J Med 1982;306:1044–1045.

37. Suttorp MJ, Kingma JH, Koomen EM, et al. Recurrence of paroxysmal atrial fibrillation or flutter after successful cardioversion in patients with normal left ventricular function. Am J Cardiol 1993;71:710–713.

38. Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA1994;271:840–844.

39. Cameron A, Schwartz MJ, Kronmal RA, et al. Prevalence and significance of atrial fibrillation in coronary artery disease (CASS registry). Am J Cardiol 1998;61:714–717.

40. Kannel WB, Abbott RD, Savage DD, et al. Epidemiological features of chronic atrial fibrillation. The Framingham Study. N Engl J Med 1982;306:1018–1022.

41. Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Arch Intern Med 1995;155:469–473.

42. Michelena HI, Ezekowitz MD. Atrial fibrillation: are there gender differences? J Gend Specif Med 2000;3:44–49.

43. Kitamura A, Shimamoto T, Doi M, et al. Secural trends in prevalence and incidence of atrial fibrillation and associated factors in a Japanese rural population. Nippon Koshu Eisei Zasshi 1991;38:95–105.

44. Leitch JW, Thomson D, Baird DK, et al. The importance of age as a predictor of atrial fibrillation and flutter after coronary artery bypass grafting. J Thorac Cardiovasc Surg 1990;100:338–342.

45. Mathew JP, Parks R, Savino JS, et al, for the Multicenter Study of Perioperative Ischemia Research Group. Atrial fibrillation following coronary artery bypass graft surgery. JAMA 1996;276:300–306.

46. Cooklin M, Gold MR. Implications and treatment of atrial fibrillation after cardiothoracic surgery. Curr Opin Cardiol 1998;13:20–28.

47. Cabin HS, Clubb S, Hall C, et al. Risk for systemic embolization of atrial fibrillation without mitral stenosis. Am J Cardiol 1990;65:1112–1116.

48. Robert M, von deer Lone E. Sex steroids and cardiac arrhythmias: More questions than answers. J Cardiovasc Electrophysiol 1998;9:665–667.

49. Paquette M, Roy D, Talajic M, et al. Role of gender and personality on quality-of-life impairment in intermittent atrial fibrillation. Am J Cardiol 2000;86:764–768.