Gender differences in cardiac electrophysiology and arrhythmias. Part 2.

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GOWDA RM, WILBUR SL, SCHWEITZER P. **Gender differences in cardiac electrophysiology and arrhythmias. Part 2.** Cardiol 2007;16(1):22–28

In part two of the Gender differences in cardiac electrophysiology and arrhythmia we are reviewing the incidence of polymorphic ventricular tachycardia, sudden cardiac death and rhythm disturbances during pregnancy. Polymorphic ventricular tachycardia and its specific form "Torsade de Pointes" is seen in patients with congenital and drug induced long QT syndrome, and in complete AV block. Regardless of it cause, polymorphic ventricular tachycardia is more common in women. On the other hand, the incidence of sudden cardiac death is higher in men than women due to higher frequency of ischemic heart disease men. In addition, sudden cardiac death is lower women regardless of age and traditional risk factors such as coronary artery disease, impaired left ventricular function and previous myocardial infarction. Left ventricular hypertrophy is an important risk factor for sudden cardiac death in women. There is no difference in the efficacy of antiarrhythmic therapy and ICDs for sudden cardiac death in men women. Atrial and ventricular premature beats are not infrequent during pregnancy while supraventricular and ventricular tachyardias are less frequent. In some patients with history of supraventricular tachyardias or Wolff-Parkinson-White syndrome pregnancy might exacerbate these rhythm disturbances. There is also some suggestion of increased risk of cardiac events in the postpartum period in patients with congenital long QT syndrome. An important management question is antiarrhythmic therapy during pregnancy because there are no entirely save antiarrhythmic drugs particularly during the first 3 months. Selective beta 1 blocking agents should be considered as the initial treatment for symptomatic arrhythmias. In hemodynamically unstable tachyarrhythmias cardioversion is save and indicated.

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. 2. časť.** Cardiol 2007;16(1):22–28

V druhej časti článku posudzujeme výskyt polymorfnej komorovej tachykardie, náhlej srdcovej smrti a porúch rytmu počas tehotenstva. Polymorfná ventrikulárna komorová tachykardia a jej špecifická forma „Torsade de pointes" sa vyskytuje u pacientov s vrodeným a liekmi vyvolaným syndrómom dlhého QT intervalu a pri úplnej AV blokáde. Bez zreteľa na príčinu polymorfná komorová tachykardia je bežnejšia u žien. Na druhej strane výskyt náhlej srdcovej smrti je vyšší u mužov ako u žien kvôli vyššiemu výskytu ischemickej choroby srdca u mužov. Náhla srdcová smrť je tiež nižšia u žien bez zreteľa na vek a tradičné rizikové faktory, ako sú choroby koronárnej artérie, poškodená funkcia ľavej komory, predchádzajúci infarkt myokardu. Hypertrofia ľavej komory je dôležitým rizikovým faktorom náhlej srdcovej smrti u žien. Medzi mužmi a ženami nie sú žiadne rozdiely v účinnosti antiarytmickej terapie a implantabilného kardioverter-defibrilátora pri náhlej srdcovej smrti. Predsieňové a komorové predčasné sťahy nie sú vzácne počas tehotenstva, kým supraventrikulárne a ventrikulárne tachykardie sú zriedkavé. U niektorých pacientiek s anamnézou supraventrikulárnej tachykardie alebo Wolff-Parkinson-White syndrómom môže tehotenstvo zhoršiť poruchy rytmu. Tiež sa uvažuje o zvýšenom riziku srdcových porúch v popôrodnom období u pacientiek s vrodeným syndrómom dlhého QT. Dôležitá je otázka manažmentu antiarytmickej terapie v tehotenstve, pretože neexistujú úplne bezpečné antiarytmické lieky najmä v prvom trimestri. Selektívne beta-1 blokátory by sa mohli podávať v začiatočnej liečbe symptomatických arytmií. Pri hemodynamicky nestabilných tachykardiách je bezpečná a indikovaná kardioverzia.

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

Polymorphic ventricular tachycardia

Polymorphic ventricular tachycardia (PVT) is characterized by continuous change in the QRS morphology at a rate between 150 to 300 bpm. PVT is mostly seen in patients with congenital or acquired long QT syndrome and less frequently in ischemic heart disease or other structural cardiac abnormalities. Dessertenne in 1966 (1) reported a specific form of PVT called Torsade de Pointes (TDP) in a patient with atrioventricular block. Among the most common causes of acquired TDP are drugs, particularly antiarrhythmic medications. Two thirds of drug induced TDP occurs in women (1). In addition to women having a prolonged baseline QT interval, the increased propensity for gender-associated differences includes differences in drug exposure, in the number of drugs prescribed, in drug pharmacology and possible differences in the way the adverse events are perceived (2). Under normal conditions genetic defects of potassium channels may be asymptomatic, but may precipitate drug-induced arrhythmias in women more frequently than in men. Men have a greater QT dispersion and women have a longer QT interval with a smaller QT dispersion (3). A longer QT minimum, as opposed to a longer QT maxi-

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Manuscript received April 8, 2005; accepted for publication August 10, 2006
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mum, is responsible for the shorter QT dispersion in women. This longer QT minimum in women may predispose to an increased risk of drug-induced torsades de pointes (3).

A review of literature on TDP cases associated with cardiac drugs showed 70% of the reported proarrhythmic cases involving women, even though only 44% of the drug prescriptions were registered to women (4). Quinidine causes greater QT prolongation in women than in men at equivalent serum concentrations (5). Dosage adjustments of quinidine based on body size alone are unlikely to substantially reduce the increased risk of TDP in women. Women at all ages have a significantly elevated risk of developing TDP as compared to men during administration of d, l-sotalol. This is age independent and not explained by differential dose-related responses in women compared to men (6, 7). Interestingly, women in the study were significantly less likely to have a history of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), and structural heart disease than men (6). Female sex preponderance in propensity of TDP was consistent over both normal and high JTc interval ranges. TDP tends to occur earlier in women than in men, and the mean heart rate in women is significantly faster than in men (6). Lehmann et al. (8) in a review of clinical trials with oral d, l sotalol (after excluding patients who developed TDP) found that in response to d, l-sotalol, the JTc intervals became longer in women than in men. This sex difference was independent of dose. Women with recent myocardial infarction and left ventricular ejection fraction of ≤ 40% have a higher d-sotalol-associated mortality (4.7 fold versus 1.4 fold compared to men) (9).

Amiodarone has very low proarrhythmic effects, regardless of gender, with a TdP incidence of < 1% (10). The incidence of polymorphic VT among patients who received ibutilide is 13.2% among women versus 3.8% among men (11). On the contrary, in another study of ibutilide, all the patients who developed polymorphic VT were men (12). However, the majority of the study population was male (90%), and the study was not powered to detect a gender difference. Dofetilide has also been associated with a female preponderance of TDP, even after adjusting for renal function (13). Regardless of gender, neither ibutilide nor dofetilide used in these studies adversely affected survival.

Other drugs reported to have a gender-influenced occurrence of TDP include (but are not limited to) terfenadine, erythromycin and probucol. Terfenadine associated TDP occurred more in women than men (15/25 cases) with total 2 deaths and both were women (14). Reinoehl et al's (15) literature analysis of QT prolongation in 359 patients who took probucol, found that women were more than twice as likely as men to experience QT interval prolongation after exposure to probucol. Ninety four percent of tachyarrhythmic events occurred in women, and TDP occurred in 69% of those patients (15). Adverse cardiac events, life-threatening ventricular arrhythmias and deaths directly related to intravenous erythromycin occurred commonly in women than men (67% versus 33%) (16). Magnitude of QT prolongation and the reverse dose dependence after receiving erythromycin is greater in females (16). Regardless of gender, significant caution must be exercised in employing drugs with the potential to cause QT prolongation.

There is an increased propensity of women to develop TdP in the setting of severe bradycardia associated with complete heart block (CHB) induced QT prolongation, even in the absence of QT prolonging drugs or electrolyte disturbances (17). Data from the National Inpatient Profile estimated a female prevalence of CHB at 52%. In cases where CHB was complicated by development of TdP, 72% were in women. The increased female preponderance noted in the clinical bradycardia model of QT prolongation with TDP strengthens the emerging association of gender differences in developing TdP in a variety of settings of QT prolongation (17). Mechanisms are more likely related to sex-dependent electrophysiologic mechanisms, than to metabolic sex differences of the QT prolonging drugs. This may be analogous to the more pronounced phenotypic expression in women of Romano-Ward long QT syndrome, despite its inheritance as an autosomal dominant trait.

Most of the studies correlating heart rate and QT interval with cardiovascular mortality have used men as their study population. A true association of female gender and increased mortality may not be entirely accurate. Schouten et al. (18) reported the duration of QT interval did not correlate with total mortality in women, as it did in men. In patients with type-1diabetes, prolonged corrected QT interval and male sex has been found to be an independent predictor of all cause and cardiovascular mortality (19). Among Finnish citizens with signs of heart disease, a prolonged QT interval predicted cardiac mortality in men, whereas a shortened QT interval predicted death in men who smoked (20). The lack of similar findings in women and healthy men may be attributed to an absence of clinical heart disease (20).

There is a female predominance of symptomatic patients with congenital long QT syndrome. Female gender is an independent risk factor for syncope and sudden death in the congenital long QT syndrome. A higher propensity toward arrhythmia in healthy females is due to

fundamental differences in repolarization and rate-corrected QT intervals, being longer in females than males. Female first degree relatives of patients with the long QT syndrome have a higher risk of cardiac events than male first or second degree relatives, independent of recorded electrocardiographic findings (21). Viskin et al., (22) reviewed the literature on congenital long QT and occurrence of TDP in the absence of arrhythmogenic drugs and found female gender to have a more potent correlation with pause dependent TDP. These findings may have important implications when using cardiac pacing for prevention of arrhythmias. Females have an increased risk of experiencing a cardiac event among long QT syndrome families; 56% of females die before 50 years of age (23). The proband (the first member of the long QT syndrome family), is more likely to be female (69%), have a higher frequency of preenrollment syncope or resuscitated cardiac arrest (80%), a resting heart rate of <60 beats/minute (31%), a prolonged QT > 500 milliseconds (52%) and a ventricular tachyarrhythmia (47%), than the unaffected family member (23). Lehmann et al., (24) found that men had significantly shorter corrected QT intervals than women in their study of long QT syndrome families linked to chromosome 11p (long QT 1) or 7q (long QT 2). Interestingly, similar sex differences were also found for the genotype-negative blood relatives, representative of the general population. In the long QT Syndrome International Registry females were found to be at higher risk for cardiac events during adulthood (25). However, the first event tended to be fatal more often in pre-pubertal males than females. Likely, the risk of fatal arrhythmic events in males decreases after puberty, associated with the physiologic shortening of the corrected QT interval. Pearl, (26) affirmed that gender, age, and heart rate should be considered when diagnosing long QT syndrome. He studied the electrocardiograms from 781 healthy children 10-18 years of age. Corrected QT intervals were significantly greater for girls than for boys in the entire population and for each age group over 14 years (26). Studies of the molecular mechanisms responsible for congenital long QT syndrome are providing insight into the potential causes of sex differences in the propensity for TDP.

Sudden cardiac death and defibrillator implant

Sudden cardiac death (SCD) is most often attributed to ventricular tachyarrhythmias. There are significant sex differences in the epidemiology of, and risk factors for, SCD, thus affecting the evaluation of interventions designed to reduce the rate of SCD. In most studies, the incidence of SCD in women is lower than in men. The Framingham study suggested that the sudden death rate, and the percentage of coronary deaths that are sudden in women, is actually lower than that in men. Roberts et al., (27) in an autopsy study demonstrated that men constitute 77% of all patients dying from coronary artery disease and 90% of patients who had SCD. Women have a lower incidence of sudden death than men in all age groups, with only 34% of coronary events leading to sudden death (28). Additionally, the traditional cardiac risk factors do not predict which women are at high risk for sudden death events. At present, it appears that left ventricular hypertrophy is a strong risk factor for SCD in women. Nulliparity, tobacco use and alcoholism might also be specific risk factors in females. On the contrary, in men, asymptomatic ventricular arrhythmias are risk factors for sudden death after myocardial infarction. The Framingham cohort (29) demonstrated a reversal of the typical male predominance of SCD when it evaluated events in the absence of known coronary artery disease, with 63% of the deaths in women, and only 44% in men.

There appears to be a lag of almost 20 years in the incidence of sudden death in women matched for standard risk factors as compared to men, but the incremental risk of SCD increases with age regardless of sex, approximately doubling with each decade in women (29). While the presence of congestive heart failure and coronary artery disease increases the risk of SCD in both sexes, the magnitude of risk is greater in men compared to women. Women with congestive heart failure experience SCD at 1/3 the rate, and those with coronary artery disease at 1/4 the rate, of men. Ventricular ectopy increases sudden death risk only in women without prior coronary heart disease (29). QT dispersion has been suggested as a means of identifying patients at risk for sustained ventricular tachyarrhythmias and sudden death. Men have a greater QT dispersion which might explain their increased risk of SCD (3).

Albert et al., (30) retrospectively studied survivors of out-of-hospital cardiac arrest referred for EP testing and found women had significantly lower incidence of coronary artery disease than men, were less likely to have suffered a prior myocardial infarction, had a higher mean left ventricular ejection fraction, were more likely to have non-inducibility for arrhythmia and were more likely to have other forms of heart disease or structurally normal hearts. Independent predictors of mortality differed between men and women. In men, a left ventricular ejection fraction of < 40% was the most powerful predictor of total and cardiac mortality, whereas in women it was

the presence of coronary artery disease (30). Among patients who have experienced aborted sudden death, men are more likely than women to have inducible monomorphic VT (31, 32). Unfortunately, the number of women represented in these studies was small, limiting their applicability to the general population. In the analysis of the Multicenter Unsustained Tachycardia trial (33), fewer women with coronary artery disease and reduced left ventricular ejection fraction had inducible sustained monomorphic VT or VF at EP testing.

A gender difference in the epidemiology of sudden death has clinical and pathophysiological implications. It is not clear whether current techniques of risk stratification and primary prevention of sudden death can be applied equally in both sexes. These strategies may be less predictive in women since sudden cardiac death is more likely to occur unexpectedly (without known coronary artery disease). A question remains whether EP testing is as useful for risk stratification in women compared to men. Kudenchuk et al., (34) studied patients who received implantable cardioverter-defibrillators (ICDs). Women required fewer devices, compared to men, for recurrent ventricular arrhythmias. They were younger than men, had a lower incidence of structural heart disease, a higher ejection fraction, low defibrillation thresholds and were more likely to have ventricular fibrillation as their device indication. There were no gender differences in the incidence of implant related complications. Another study by Horton et al. found no differences between women and men in the rates of recommendation for an ICD however more women refused device implantation than men and they were more often considered medically ineligible for implantation (35). This combination resulted in fewer women receiving ICDs than men (35). Engelstein et al., (36) in their data from the antiarrhythmics versus implantable defibrillators study (AVID) also found similar gender differences. In spite of better overall left ventricular ejection fractions, there was an increased female incidence of idiopathic VF and congestive heart failure. However, women comprised only 24% of those studied. At present, guidelines for ICD implantation appear to apply equally to both sexes with malignant ventricular arrhythmias; although the percentages of device indications may vary depending on gender and associated etiology of their arrhythmia indicator.

Arrhythmias in pregnancy

Atrial and ventricular premature beats are frequently present during pregnancy and are usually benign (37). Although SVT and malignant ventricular tachyarrhythmias occur less frequently, they can often increase in frequency and duration during gestation. Incidence of arrhythmias is increased in pregnant women with or without concomitant organic heart disease (37). Pregnancy may complicate the invasive evaluation of arrhythmias and raise special considerations for their treatment. In 1956, Mendelson (38) was one of the first to report on the occurrence of SVT during pregnancy. There are several studies with conflicting results of the prevalence and severity of paroxysmal SVT in pregnancy (37 – 41). A few small studies suggest a high probability of onset of paroxysmal SVT during pregnancy (38 – 40), but a larger study cited a low probability that a first paroxysmal SVT will occur during pregnancy (41). Due to radiation concerns, there are no large studies correlating symptoms or ECG documented arrhythmias with invasive EP evaluation. Widerhorn et al., (39) described three patients with stable SVT and Wolff-Parkinson-White syndrome who had a marked increase in the frequency of arrhythmias during pregnancy. Tawam et al., (40) found an increased risk of both exacerbation, most often during the first trimester, and new onset of SVT during pregnancy. Lee et al., (41) observed that the negative relative risk of onset of paroxysmal SVT during pregnancy was more powerful for those with AVNRT than those with accessory pathways.

Rashba et al., (42) analyzed women with long QT syndrome and found a significant increase in the risk of cardiac events in the postpartum period, but not during pregnancy. Increased heart rate secondary to pregnancy may have a protective effect. With the decrease in the heart rate after delivery, there is likely an increase in the QT interval. There are also reports suggesting new-onset ventricular arrhythmias during pregnancy (43). Brodsky et al., (43) reported four pregnant women who had VT at presentation, without evidence of structural heart disease or previous arrhythmia. Most patients respond to beta-blocker therapy and in most patients Holter monitoring and EP after delivery fail to induce an arrhythmia.

The mechanism of the exacerbation of clinical rhythm disturbances during pregnancy is largely unknown (37). Possible explanations for this increased propensity for arrhythmias during pregnancy include changes in autonomic tone, neurohumoral, direct cardiac electrophysiologic effects of hormones, hemodynamic changes and emotional changes (44). Pregnancy by itself may have an arrhythmogenic effect (44). Also, increased medical attention for minor symptoms by pregnant women may give opportunity to diagnose rhythm disturbances otherwise not seen.

Special attention should be paid to anti-arrhythmic therapy during pregnancy (37). It seems prudent to avo-

id hemodynamically significant arrhythmias, for possible fetal harm during hypotensive spells. However, antiarrhythmic therapy may have fetal effects and there are documented risks with fetal radiologic exposure, such as during invasive EP testing. Non-urgent radiologic testing should be avoided if possible and appropriate counseling of patients before fluoroscopic radiologic studies is critical (45). No drug is entirely safe in pregnancy. Electrical cardioversion is necessary in all patients who are hemodynamically unstable. In stable patients with SVT, the initial therapy includes the vagal maneuvers to terminate breakthrough tachycardias. For short-term management, when the vagal maneuver fails, intravenous adenosine is the first-choice drug and may safely terminate the arrhythmia. In hemodynamically stable patients with ventricular tachyarrhythmia, initial therapy is with procainamide or lidocaine. If prophylactic therapy is needed, beta-blocking agents with beta-1 selectivity are considered as first-choice drugs (43, 44, 46). If this therapy is ineffective, and for long-term therapy, beta-blocking agents with beta-1 selectivity are first-line drugs; class IC agents or the class III drug, sotalol, are therapeutic alternatives. Although there is conflicting data, digoxin and beta-blockers are probably safe in pregnancy (43). Continuation of beta-blocker therapy during pregnancy and the postpartum period in women with long QT syndrome is suggested (42). Amiodarone and sotalol have been used during pregnancy. In patients with syncope and ventricular tachyarrhythmia or aborted sudden death, an ICD is indicated.

Natale et al. (47) evaluated ICDs and outcome of pregnancy. The majority of patients had epicardial devices. There was no increased risk of major ICD related complications. They suggest that women with defibrillators can consider pregnancy unless otherwise contraindicated by underlying structural heart disease. In patients with symptomatic bradycardia, a pacemaker can also be implanted using echocardiography or epicardially to avoid radiation exposure.

The treatment of the pregnant patient with cardiac arrhythmias requires important modification of the standard practice of arrhythmia management. The goal of therapy is to protect the patient and fetus until delivery. Subsequently, chronic or definitive therapy can be administered. Ideally, it is optimal to avoid anything that could affect the fetus including drugs and/or radiation. Possible interventions include vagal maneuvers and dietary modification (elimination of ethanol, caffeine, tobacco, etc.). However, sometimes arrhythmias that are compromising to both the mother and baby persist, which necessitates intervention. At present, the second line of intervention is drug therapy. In exceptional cases, it may be necessary to perform EP testing, radiofrequency catheter ablation, or device implantation.

Clinical implications

Recently there is increased awareness of the impact of gender on cardiac arrhythmias e.g., drugs that prolong repolarization induce torsade de pointes more frequently in women than men; female gender is an independent risk factor for syncope and sudden death in the congenital long QT syndrome; and the higher propensity toward arrhythmia in women without structural heart disease is associated with fundamental differences in repolarization such that rate-corrected QT intervals are longer in females than males. Women appear to be less vulnerable to sudden death than men at any level of multivariate risk. Defibrillators appear to be equally safe and efficacious in men and women. Mechanisms underlying these differences are incompletely defined but are believed to include gonadal steroids, autonomic properties, and possible differences in electrolyte channel density or function. Implications for patient care include maintaining close monitoring of the QTc interval when administering antiarrhythmic agents, especially in women because of their baseline longer QT intervals. ECG monitoring of pregnant patients is imperative if a history of hemodynamically compromising, possible lethal arrhythmias, or prolonged QTc is known or suspected.

Conclusion

Numerous research studies have been performed to evaluate the effects, dangers, complications, and contributing factors for cardiac arrhythmias. Few studies, however, have focused primarily on women. Occasionally, studies may contain small secondary statements about sexual differences, but in-depth research regarding arrhythmias in women is lacking. Furthermore, research findings vary among authors and often present conflicting information. Further studies are needed to evaluate the role of heart disease and arrhythmias in women and to determine if therapies for arrhythmias should be gender specific.

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