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The effects of menstrual cycle on cardiac conduction system

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The Effects of Menstrual Cycle on Cardiac Conduction System

Women's cardiac conduction system shows some physiological differences compared to men's. Resting heart rate is higher and QT and corrected QT (QTc) intervals are longer in women. Additionally, female gender is an independent risk factor for drug-related torsades de pointes and congenital long QT syndrome (1). Sudden cardiac death incidence is higher in women when excluding coronary artery disease and structural heart diseases (2). QT interval defines the duration from the beginning of the QRS complex until the end of the T wave and refers to the period of ventricular myocardium activation and repolarization. It may vary according to age, gender, pregnancy condition and the heart rate (3). QT prolongation and shortening may reflect some pathological conditions. QT prolongation occurs in ischemic heart disease, cardiomyopathy, mitral valve prolapse and the use of certain anti-arrhythmic drugs. QT shortening is seen in patients with hypercalcemia and under digitalis treatment. Prolongation of the QT interval can lead to fatal arrhythmias such as ventricular tachycardia and ventricular fibrillation.

Longer QT interval is seen with puberty and recovers after menopause (4,5). These data suggest that, sex hormones may be effective on the QT interval and other repolarization parameters. Additionally some studies showed that, autonomic blockade with atropin and propranolol did not alter intersexual QT interval differences thus supports the relationship between sex hormones and ventricular repolarization disparity (6). During the menstrual cycle, estradiol levels start to rise with follicular phase and remains high until the ovulation. After ovulation, estradiol levels decrease and progesterone levels become higher in the luteal phase. Estradiol and progesterone have opposite effects on cardiac conduction system. Biological effects of estrogen occur by alpha and beta estrogen receptors. These receptors are located at cardiac myocytes, fibroblasts and endothelial cells (7,8). Estrogen receptors are located both in the cytosol and nuclear compartment. While effects of estrogen on the nuclear receptors (called genomic effects) may occur during the hours-days, effects on cytosolic receptors (non-genomic effects) may be seen in seconds. Estrogen has negative inotropic effect on heart (9). This effect occurs via voltage dependent L-type calcium channel inhibition and decrease of inward calcium flux. Moreover, estrogen exhibits calcium antagonist effect by affecting Na^+/Ca^{2+} exchange (10). Additionally, estrogen supresses the activity of T-type calcium currents, which is important for pacemaker activity, thus leads to negative chronotropic effects (11,12). While some studies have shown that estrogen decreases potassium channel flow in the third phase of the action potential so causes to QT prolongation (13), some suggest that there is no effect on cardiac repolarization (14). Progesterone is a 21-carbon steroid and produced by corpus luteum, placenta and a small amount of follicles. Its concentrations are high during the luteal phase. Progesterone receptors are located at vascular smooth muscle cells, endothelial cells cardiac myocytes and left atrial appendage myocytes (15-17). Although we have limited data on the effect of progesterone on cardiovascular system, it is thought that progesterone has the opposite effects of estrogen. QT interval is shorter during the luteal phase when progesterone level is high (18,19). Progesterone increases the slowly activated late rectifier potassium current and inhibits L-type calcium channel currents (20). These effects explains why the action potential duration is shorter during luteal phase. Furthermore, these mechanisms reveal the reason of QT interval shortening effects.

The study results of QT interval changes during the menstrual cycle are conflicting. In general, it can be said that QT interval does not change during the menstrual cycle (14,19), some studies have shown that QT interval shortens during luteal phase with high progesterone levels (18). In addition, in case of exposure to QT prolonging drug, QT prolongation was shown to be greater in ovulatory phase than in luteal phase (19). Progesterone and progesterone/estradiol ratio is inversely proportional with the drug associated QT prolongation, that suggests a protec-

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tive role of progesterone (19,21,22). These studies support that estrogen prolongs the QT interval and progesterone shortens.

Ventricular Arrhythmias and Sudden Cardiac Death

Women are less prone to ventricular arrhythmias except torsades de pointes and drug-related ventricular arrhythmias. Sudden cardiac death is defined as death within one hour of symptom onset without any reason, and it is rare in women (23). The reason is not known exactly but lower prevalence of coronary artery disease or less susceptibility to ventricular arrhythmias may be resulted to these gender differences. Ventricular tachycardia (VT) or ventricular fibrillation (VF) is less common in women even if similar ejection fraction, the number of coronary artery disease and myocardial infarction history cases (24). Less VT/VF experience have been identified in women patients with coronary artery disease with implantable cardioverter defibrillator (25).

Animal models suggest that estrogen has protective effects against ventricular arrhythmias. Post-infarction ventricular arrhythmias are less common in rats treated with estrogen (26). Additionally, acute estrogen administration to female rats has revealed protective effects on ischemia related ventricular arrhythmias by calcium channel blocking (27). Furthermore, estrogen administration to dogs of both sexes has been shown to reduce reperfusion related arrhythmias, via nitric oxide release and opening of calcium-activated potassium channels (28).

Some studies have shown that QT interval changes occur during the menstrual cycle and this fluctuations may lead to the risk of arrhythmias in different menstrual phases (29). Nakagawa et al suggested that QT interval is approximately 10 milliseconds shorter in luteal phase and this is the result of progesterone dominance in contrast to estrogen's QT prolonging effect (18). In contrast, some studies showed that there is no significant changes in QT interval with the menstrual cycle (6,14,19). This mismatch in these studies may be due to collected data of patients was not enough to be responsive to individual differences in QT interval and may be unable to sufficiently take into account the biological variables. More comprehensive studies are needed to clarify the effects of sex hormones on cardiac conduction system.

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Conflict of Interests

The authors declare that they have no conflict of interest. We certify that we had no relationship with companies that may have a financial interest.

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