Invited Commentary

Invited Commentary: Sex-Steroid Hormones and QT-Interval Duration

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In this issue of the Journal, Zhang et al. (Am J Epidemiol. 2011;174(4):403–411) make a substantial contribution to research in the area of hormonal influences on cardiac repolarization by demonstrating an inverse association between testosterone levels and the Bazett's adjusted QT interval (QTc) and RR-adjusted QT interval in men but not in postmenopausal women. They suggest that testosterone levels might explain the difference in QTc-interval duration between men and women and could contribute to population variability in QTc-interval duration among men. In this commentary, the gender difference and the role of testosterone in human cardiac repolarization are addressed. In addition, the gender differences in the congenital long-QT syndrome, drug-induced ventricular arrhythmias, and sudden cardiac death are discussed.

gonadal steroid hormones; long QT syndrome; testosterone

Abbreviations: hERG, human ether-a-go-go-related gene; LQTS, long-QT syndrome; MESA, Multi-Ethnic Study of Atherosclerosis; NHANES III, Third National Health and Nutrition Examination Survey; QTc, heart rate-corrected QT.

Sudden cardiac death accounts for approximately 50% of cardiovascular deaths and 20% of all deaths (1–3). Nearly 85% of sudden cardiac deaths are caused by ventricular arrhythmias (4). An important cause of ventricular arrhythmia is prolongation of ventricular repolarization, which is reflected by a longer QT interval on an electrocardiogram. The QT interval is measured from the Q-top (the beginning of the QRS complex) to the end of the T wave (5, 6). Prolongation of ventricular repolarization could result in early afterdepolarizations, which in turn may induce reentry and thereby provoke torsade de pointes and fatal ventricular arrhythmias (7–10).

GENDER DIFFERENCES IN CARDIAC REPOLARIZATION

A gender difference in human cardiac repolarization was first described in 1920 by Bazett (11). This difference is demonstrated by a longer heart-rate-corrected QT (QTc) interval in females (12). In 1992, in a large study of 14,379 children and adults, investigators demonstrated that the gender differences in the QTc interval were not present in young children (13). However, the QTc intervals of females were significantly longer than those of males between 15 and 50 years of age. This difference was due to a 20-ms decrease in the QTc intervals of adolescent males after puberty. The QTc intervals of females remained unchanged during childhood and adolescence, which resulted in longer QTc intervals in adult females (13–15). These gender differences decrease with age, which is illustrated in Figure 1 (13). Because the period between puberty and 50 years of age coincides with the highest circulating levels of androgens in males, it was soon hypothesized that male sex hormones might play a role in the shorter QTc interval in males. Furthermore, virilized females exhibit QTc intervals similar to those of healthy males, whereas castrated males have QTc intervals similar to those of healthy females (16). Testosterone therapy also reduces QT dispersion in males with congestive heart failure (17). Recently, the Testosterone in Older Men With Mobility Limitations trial, which included 209 community-dwelling males, was discontinued earlier than planned because there was a significantly higher rate of adverse cardiovascular events in the testosterone group than in the placebo group (18).
In this issue of the Journal, Zhang et al. (19) present findings from the Third National Health and Nutrition Examination Survey (NHANES III) and the Multi-Ethnic Study of Atherosclerosis (MESA) suggesting that testosterone levels may explain the difference in QTc-interval duration between males and females could be a contributor to population variability in QTc-interval duration among males. They found an inverse association between serum testosterone levels and QTc interval in males but not in postmenopausal females. The latter finding could possibly be explained by the fact that testosterone levels in females are much lower than those in males, thereby preventing a notable difference between the highest and lowest levels in the study. In addition, the association between testosterone level and the QTc interval was more prominent in males from NHANES III than in those from MESA. This could be explained by the fact that NHANES III included men aged 40 years or older, whereas MESA participants were 45 years of age or older. The NHANES III men, who were on average 8 years younger than the MESA men, had higher testosterone levels. The extent to which an ethnic difference between the males from NHANES III and MESA played a role is unclear. The findings from Zhang et al. are in agreement with previous findings from the Rotterdam Study and the Study of Health in Pomerania, in which van Noord et al. (20) reported an inverse association between total testosterone levels and QTc intervals in the general population.

GENDER DIFFERENCES IN DRUG-INDUCED VENTRICULAR ARRHYTHMIAS

In the past 2 decades, a number of drugs have been withdrawn from the market or restricted in use because they caused drug-induced torsade de pointes (7–10). The first study showing that females experience drug-induced torsade de pointes more often than males was published in 1993 (28). This retrospective study focused on drugs for cardiovascular indications. In 2002, Bednar et al. (29) presented data showing that nonantiarrhythmic drugs were more likely to cause torsade de pointes in females than in males. Other risk factors that predispose individuals to torsade de pointes, such as hypokalemia, hypomagnesemia, or use of digoxin, do not account for the gender differences in rates of drug-induced ventricular arrhythmia (28, 30). Another explanation for the gender differences could be thyroid dysfunction, which is more common in females and can itself cause QTc prolongation and torsade de pointes (28, 31–34). However, thyroid dysfunction was found in only 10% of females with drug-induced torsade de pointes, and a similar incidence of thyroid dysfunction was found among males with torsade de pointes (35). Therefore, it is unlikely that thyroid dysfunction contributes to gender differences in drug-induced torsade de pointes. Interestingly, erythromycin led to a similar number of arrhythmic events in males and females before the age of 10 years. It should be taken into account that the number of events before 10 years of age was low. In females, from 10 to approximately 50 years of age, there were more arrhythmic events than in males who were the same age. This difference disappeared after the age of 60 years (36).

Virtually all drugs that prolong the QT interval block a specific potassium current, the rapid component of the delayed rectifier (37). The rapid component of the delayed rectifier is generated by expression of the human ether-à-go-go-related gene (hERG), which conducts potassium ions out of cardiomyocytes and is responsible for timely repolarization (38). Recently, a study was published that indicated that current use of noncardiovascular hERG-encoded potassium channel-inhibiting drugs in the general population was 1 in 2,000–2,500 livebirths (21, 22). The autosomal-dominant form (Romano-Ward syndrome) is far more common than the recessive form, which is associated with deafness (Jervell and Lange-Nielsen syndrome) (23). The most prevalent forms of LQTS are LQT1 (KCNQ1) and LQT2 (KCNH2), which are due to mutations in potassium channels, and LQT3 (SCN5A), which is due to a sodium channel mutation (24). In LQT1 and LQT2, females have a longer QTc interval than do males after the age of 16 years, but no gender differences are present before the age of 16 years (25). Furthermore, during childhood, the risk of ventricular arrhythmias is significantly higher in males than in females with LQT1, whereas there is no gender difference in LQT2 or LQT3. During adulthood, females with LQT1 and LQT2 experience ventricular arrhythmias more often than do males (26). The International Long-QT Syndrome Registry noted that the first ventricular arrhythmia occurred after the age of 15 years in only 8% of males but in 40% of females (27).

GENDER DIFFERENCES IN CONGENITAL LONG-QT SYNDROME

Congenital long-QT syndrome (LQTS) is an inherited disease characterized by prolongation of ventricular repolarization, which is manifest by QT prolongation, episodes of syncope, malignant ventricular tachycardia, and fibrillation (6). The prevalence of LQTS is estimated to be approximately 1 in 2,000–2,500 livebirths (21, 22). The autosomal-dominant form (Romano-Ward syndrome) is far more common than the recessive form, which is associated with deafness (Jervell and Lange-Nielsen syndrome) (23). The most prevalent forms of LQTS are LQT1 (KCNQ1) and LQT2 (KCNH2), which are due to mutations in potassium channels, and LQT3 (SCN5A), which is due to a sodium channel mutation (24). In LQT1 and LQT2, females have a longer QTc interval than do males after the age of 16 years, but no gender differences are present before the age of 16 years (25). Furthermore, during childhood, the risk of ventricular arrhythmias is significantly higher in males than in females with LQT1, whereas there is no gender difference in LQT2 or LQT3. During adulthood, females with LQT1 and LQT2 experience ventricular arrhythmias more often than do males (26). The International Long-QT Syndrome Registry noted that the first ventricular arrhythmia occurred after the age of 15 years in only 8% of males but in 40% of females (27).

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associated with an increased risk of sudden cardiac death. This risk tended to be higher in females than in males (39). The mechanisms underlying these differences are not fully understood. Some drugs have narrow margins between the plasma concentrations required to achieve a therapeutic effect and those associated with toxicity (40). Pharmacokinetic and pharmacodynamic interactions differ for males and females (e.g., CYP3A4 exhibits higher activity in females than in males, whereas the activities of CYP1A2, 2C9, 2C19, 2D6, and 2E1 are higher in males than in females) (41). Furthermore, the metabolism of many drugs (e.g., erythromycin) has been reported to show gender differences in clearance (41). In addition, sex steroids themselves influence cardiac potassium channels. Shuba et al. (42) showed that testosterone could protect against drug-induced arrhythmia (42).

GENDER DIFFERENCES IN SUDDEN CARDIAC DEATH

Although the majority of sudden cardiac deaths are caused by ventricular arrhythmias (4) and torsade de pointes is more prevalent in females than in males in both the congenital and acquired (including drug-induced) forms of LQTS (12, 28, 43–45), sudden cardiac death is more prevalent in males than in females (46, 47). This gender difference in sudden cardiac death can in part be explained by gender-related differences in the onset of coronary heart disease and heart failure, the latter of which is an especially strong risk factor (46–48).

Zhang et al. (19) confirmed an inverse association between testosterone levels and the QTc interval in a well-performed analysis of 2 populations. They suggested that testosterone levels may explain the differences in the QTc-interval duration between males and females that could contribute to population variability in QTc-interval duration among males. This work is an important addition to previous reported literature regarding the gender difference in human cardiac repolarization (11) and the suggestion that male sex hormones may play a role in the shorter QTc interval in males, as the period between puberty and 50 years of age coincides with the highest circulating levels of androgens in males (13). Because Zhang et al.’s study was cross-sectional, a next step might come from repeated measurements from follow-up data. Also, the future might tell us how these important findings fit into the complex genetic and environmental etiology of repolarization disturbances and their adverse cardiovascular consequences.

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