Age and Gender Modulation of the Long QT Syndrome Phenotype

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KEYWORDS

• Long QT • Gender • Repolarization • Sudden death
• Syncope • Hormonal

Recent literature points to a complex relationship between gender, age, and long QT syndrome (LQTS), both congenital and acquired. Understanding of this complex relationship is essential for the clinician because it plays an important role in clinical outcomes. Importantly, both syncope and sudden death in LQTS are affected by the presence or absence of sex hormones. In this article, we begin with a review of the manner in which age and gender affect electrocardiographic (ECG) measurements of repolarization and therefore the QT interval. We detail the effects of age and gender on clinical outcomes and review how these modulations drive treatment recommendations. We also discuss basic research that has recently begun to shed light on these clinical phenomena and may give insight into potential future treatments.

REVIEW OF HUMAN SEX HORMONE PHYSIOLOGY

To understand how gender and age modulate the QT interval and therefore LQTS, we first briefly summarize the progression of human sex hormone exposure in men and women throughout the basic stages of life. In men, the testes secrete androgens, including androstenedione; dihydrotestosterone; and, much more abundantly, testosterone. Estrogens are produced in men as well, although at an estimated 20% of that in a nonpregnant woman. The majority of the estrogen in men comes from conversion of testosterone and androstenediol to estrogens in somatic tissue.[1,2]

The interstitial cells of Leydig within the testes begin to produce testosterone at around the seventh week of embryonic life. Ten weeks after birth, testosterone secretion shuts down and little measurable testosterone is produced until puberty. At puberty, there is a steep increase to a peak production of nearly 7000 μg/d of testosterone in young adulthood. Thereafter, there is a steady decline of production reaching 20% to 50% of peak values by age 80 years.[1,3,4]

In women, the theca cells of the ovary produce androstenedione and testosterone, although the majority of the androgens produced undergo conversion within the ovary into, primarily, estrogens. Thus, ovaries produce only 7% of the androgens seen in males. The granulosa cells produce estrogens and progestins. Estrogen production is at a minimum in women until the monthly hormonal cycles begin at puberty. During young adulthood, estrogen secretion cycles between 100 and 300 μg/d.[1] At menopause, there is a steady decline of estrogen in a fluctuating pattern until a minimum is reached. Decline in progesterone production is more rapid.[5–8] Furthermore, androgen levels decrease dramatically, with onset of reduction occurring before menopause. The androgens that are produced are heavily converted

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to estrogens in adipose tissue. Thus, the postmenopausal hormonal state is one of low progesterone and androgen levels and reduced but measurable estrogen levels.

During pregnancy, estrogen and progesterone levels increase significantly as a result of placental secretion. Estrogen increases to a level of 30 times more than normal levels, although the potency of the primary estrogen produced (estriol) is significantly lower than that of estradiol. Progesterone is also produced in vast quantities during pregnancy, averaging 0.25 gm/d toward the end of pregnancy. In the postpartum period, there is a rapid decline of hormones to levels lower than the nonpregnant state. Breastfeeding prolongs this suppressed state.[1,9,10]

AGE AND GENDER EFFECTS ON CLINICAL ECG

In the 1920s, Bazett noted that the QT interval was longer in women. Early population studies of repolarization in humans as measured by the QT interval revealed longer QT intervals in women than in men. With ECG data from more than 400 normal men and women with a mean age of 40 years, Merri and colleagues[11] demonstrated that the mean QTc interval was 12 milliseconds (ms) longer in woman than men. Evidence of sex hormone effect on QTc is observed when QTc is compared at the various phases of the ovulatory cycle in women after autonomic blockade with atropine and propranolol. During the follicular phase, marked by an increase in estrogen alone, women have a longer QTc interval than in the luteal phase, which is associated with an increase in progesterone levels and a more modest increase in estrogen levels.[12] This finding was echoed by Rodriguez and colleagues[13] who showed that the QT response to ibutilide infusion varied depending on subjects' menstrual cycle. Again, the luteal phase was protective against QT prolongation in these female subjects. More recent population data underscore the underlying hormonal effect on QT. Kadish and colleagues[14] demonstrated that QT intervals of postmenopausal women treated with estrogen-only hormone replacement therapy were significantly longer than those of women treated with estrogen-progesterone combined therapy.

Age adds an additional dimension to the gender-QT interaction. During infancy and childhood, the QTc interval appears no different between boys and girls. With the onset of puberty, the QTc shortens in men by 20 ms (**Fig. 1**), whereas in women it appears stable through sexual maturation.[15] The longer QTc in women appears to be maintained throughout adulthood,[16,17] although the difference diminishes significantly after age 50 years.[17] Importantly, both

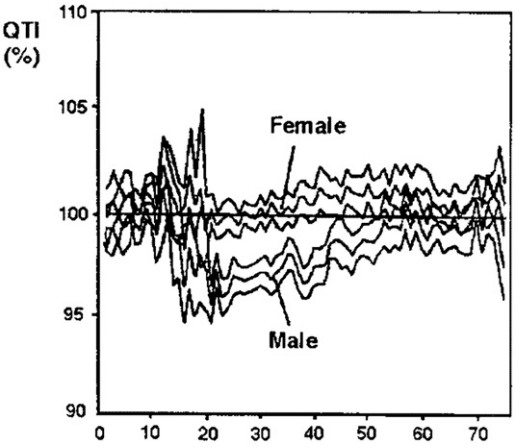

Fig. 1. Effect of age on QT in men and women. QT index (QTi = QT measured/QT expected) plotted for men and women from birth to age 70 years. For both genders, the 3 lines plotted represent the mean QTi (*middle line*) along with the upper and lower standard deviations of the mean. Of note, at puberty, the QT index of men is significantly reduced compared with that of women. The QT index of men and women do not overlap again until after age 50 years. (*From* 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(7): 693; with permission.)

men and women see prolongation of their QT interval with increase in age in late adulthood. The mean QTc appears to increase 1 ms for each decade of life after age 50 years.[18]

Several other important differences are seen with respect to repolarization and gender. First, the shape of the T wave changes with respect to gender and exposure to sex hormones. Women have lower-amplitude T waves by 25% compared with that in men.[19] Furthermore, both the ascending and descending limbs of the T-wave slope are flatter in women than in men. This pattern appears to reverse when comparing women with virilization syndrome with castrated men.[20,21] On 24-hour Holter monitoring, the QT-RR relationship is different between men and women. Regardless of which aspect of the T-wave is used, the slope of the QT-RR linear regression is steeper in women.[22] Recent data confirm this finding (**Fig. 2**).[23] These differences reflect important physiologic differences between cardiac repolarization in men and women. In the next section, we explore the basic mechanisms underlying these differences that directly affect the phenotype in LQTS.

BASIC MECHANISMS

Receptors to estrogen, androgens, and progesterone have all been demonstrated in cardiac