Journal of the American Heart Association

EDITORIAL

The Role of Testosterone and Gonadotropins in Arrhythmogenesis

Arja S. Vink, MD, MSc; Pieter G. Postema, MD, PhD

Nearly 100 years ago, prof. Henry Bazett described a shorter heart rate corrected QT interval (QTc) in adult men compared with women. In the past decades, we have learned that this difference is not present during the first months of life but arises during puberty. Throughout puberty, the QTc shortens in male but not in female adolescents. This sex difference decreases with age during adulthood because of progressive QTc lengthening in men. As a result, no clear sex differences are present in the age group of >60 years. It is thus thought that sex hormones play a role in the relationship between QTc, age, and sex. However, the mechanisms underlying the influence of sex hormones on the repolarization are complex and still incompletely resolved. It has been suggested that the presence of nuclear and cytosolic receptors for sex hormones within the cardiovascular system and neuroregulatory tissues[1] exerts direct and indirect effects on the cardiovascular system and may regulate gene expression. From observational studies, we have learned that testosterone decreases the L-type calcium current and increases certain potassium channel currents, and may shorten the action potential and consequently QTc through these mechanisms.[2] The concentration of testosterone is regulated by the hypothalamic-pituitary-gonadal axis. During puberty, the hypothalamic-pituitary-gonadal axis becomes activated[3] and therefore a higher concentration of testosterone is found during this period compared with childhood, presumably resulting in a QTc shortening in male subjects. In adulthood, the level of testosterone gradually decreases with age in men,[4] explaining why with aging, the QTc in men gradually lengthens and approximates that of women. What makes the influence of sex hormones on the repolarization even more complex is that there also seems to be an interaction between sex hormones and gonadotropins. Especially, follicle-stimulating hormone (FSH) appears to independently prolong ventricular repolarization, resulting in QTc prolongation, although the exact mechanisms by which the ion currents involved in cardiac repolarization are affected are still under study.[5] In secondary hypogonadotropic hypogonadal men (presenting with both low FSH and testosterone concentrations), no difference in QTc was seen compared with healthy controls, which could be because of opposing actions of low FSH and low testosterone on repolarization.[6] In contrast, men with peripheral hypogonadism (presenting with high FSH and low testosterone concentrations) had longer QTc compared with healthy men.[7]

See Article by Hasegawa et al.

Age- and sex-related differences in QT-related arrhythmogenesis are most clear from previous studies in patients with long-QT syndrome (LQTS) who have a genetically determined impaired repolarization reserve. The genesis of LQTS-related cardiac events is largely dependent on the degree of QTc prolongation, indeed with a complex interaction with age, sex, and genotype.[8] As an example, boys with LQTS type 1 have a >2-fold increased QT-related cardiac event risk compared with girls, whereas after the onset of puberty the risk for events is similar for both male and female

Key Words: Editorials ■ QT interval electrocardiography ■ sex differences ■ testosterone ■ torsade de pointes

Correspondence to: Pieter G. Postema, MD, PhD, Department of Clinical and Experimental Cardiology, Heart Center, Amsterdam University Medical Centers, Meibergdreef 9, Amsterdam, N/A 1105AZ, the Netherlands. E-mail: p.g.postema@amsterdamumc.nl

For Disclosures, see page 3.

JAHA is available at: www.ahajournals.org/journal/jaha

subjects. In patients with LQTS type 2, boy and girl event rates are similar, but female subjects with LQTS type 2 have a higher event rate after the onset of puberty compared with male subjects.[9] Hence, sudden changes in concentrations of sex hormones appear to modulate arrhythmogenesis in these patients, because changes in events appear during/after the onset of puberty. A differing sensitivity to changes in sex hormone concentrations between these genotypes is furthermore suspected, as female subjects with LQTS type 2 (impaired function of HERG Kv11.1 channels responsible for the rapid delayed rectifier current I_{Kr}) experience more cardiac events than female subjects with LQTS type 1 (impaired function of Kv7.1 channels responsible for the slow delayed rectifier current I_{Ks}) after puberty. Indeed, there appears to be differential sensitivity of these channels to different sex hormones, like testosterone, estrogen, and progesterone. This hypothesis is underscored by the observation that women with LQTS type 2 encounter a significantly increased event risk during other periods of sudden changes in sex hormone concentrations (eg, during the puerperium, 9 months postpartum, and the perimenopausal and postmenopausal periods).[10–12]

Another clinical "model" of the influence of sex hormones on QTc to increase our insights in QT-related arrhythmogenesis comprises deliberate interactions with the hormonal system. In this issue of the *Journal of the American Heart Association* (*JAHA*), Hasegawa and colleagues[13] did just that. They show that medical castration in men with prostate cancer, thereby suppressing testosterone with gonadotropin-releasing hormone analogues, prolongs the QTc (416±27 ms to 439±31 ms; $P<0.001$). In general, the extent of QTc prolongation was modest and not clinically relevant. However, 2 patients had QT-related arrhythmia (torsades de pointes [TdP]) >6 months after receiving medical castration. Although the incidence of a prolonged QTc was similar between the patients with and without TdP, patients with TdP nevertheless had a greater increase in QTc (ΔQTc) during therapy compared with the pretherapy baseline value. From a previous study on men with endocrine hypogonadism and acquired LQTS who developed TdP, we learned that hypogonadism also appears to alter the T-wave morphological features beyond simple QTc prolongation.[14] Similarly, the 70-year-old man, who is described in more detail by Hasegawa and colleagues, showed abnormal T-wave morphological features and possibly also larger U-waves in V2 to V4, a phenomenon that can also be seen in patients with LQTS.[15,16] Both the larger magnitude of the ΔQTc as well as the abnormal T-wave morphological features indicate abnormal repolarization reserve and larger repolarization heterogeneity in the patients who developed TdP during therapy with gonadotropin-releasing hormone analogues, compared with the patients who did not develop TdP. As also suggested by the authors, it is possible that in this group of men aged ≈75 years (in whom levels of testosterone are naturally decreasing, resulting in a gradual prolongation of the QTc), differing sensitivity to changes in testosterone and FSH concentrations is present compared with male patients aged <60 years. This hypothesis is reinforced by previous data in hospitalized patients receiving QTc-prolonging agents, showing that TdP is more common in older (aged >65 years) than in younger patients.[17] In addition, also in patients with LQTS, it is well known that there are differences in the amount of QT prolongation and the susceptibility to cardiac events, which are in part explained by genetic variability between individuals.[18] Such variability will undoubtedly also play an important role outside LQTS, and will likely explain part of the observed variability by Hasegawa and colleagues.

Medical castration, suppressing testosterone with gonadotropin-releasing hormone analogues, can thus not only cause QTc prolongation but also malignant QT-related arrhythmia. Noteworthy, an accompanying effect of medical castration is modulation of the ST segment. Low testosterone concentrations seem to decrease ST segments: in secondary hypogonadotropic hypogonadal men and (medically) castrated men, the J-point amplitude is significantly lower compared with healthy men[6,7]; and in patients with prostate cancer with asymptomatic Brugada syndrome, the typical coved-type ST-segment elevation disappeared after orchiectomy.[19] Interestingly, in one study, men with Brugada syndrome manifested significantly higher testosterone levels than healthy men.[20] Surgical of medical castration may therefore be of value in preventing malignant ST-segment related arrhythmias. The exact mechanisms by which this occurs are also not yet explained. It has been observed that testosterone alters the Kv4.3 channel responsible for the transient outward current I_{to}, which could have a role in Brugada syndrome, but whether there is also an effect on the Nav1.5 channel responsible for the fast inward depolarizing sodium current I_{Na} is currently unclear.

Taken together, Hasegawa and colleagues showed us that especially in older male patients who receive medical castration, QTc monitoring is mandatory to prevent severe QTc prolongation and prevent malignant QT-related arrhythmias. As mentioned before, the extent of QTc prolongation following medical castration may be small and not clinically relevant in most patients; it may, however, lead to dangerous QT prolongation in individuals who have a reduced repolarization reserve, either genetically or secondary to the use of QT-prolonging drugs. In the absence of specific measures for different patient categories, general precautions would apply to this finding: when the QTc is >500 ms or if there has been an increase of at

least 60 ms compared with baseline values, additional awareness should emerge. This involves evaluations on other QT-prolonging drugs (considering the possibilities to limit drug exposure), potassium plasma levels (considering the possibilities to increase plasma levels and thereby reduce the QT interval), and continuation of the testosterone suppression (discontinuing or lowering of the therapy should be considered). The latter is also not a simple task as a certain chance of malignant arrhythmias versus incomplete suppression of prostate cancer needs delicate balancing, preferably together with the patient.

ARTICLE INFORMATION

Affiliations

From the Department of Clinical and Experimental Cardiology, Amsterdam University Medical Centers, University of Amsterdam, Heart Center, Amsterdam, the Netherlands (A.S.V., P.G.P.); and Department of Pediatric Cardiology, Emma Children's Hospital, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands (A.S.V.).

Disclosures

None.

REFERENCES

1. Stumpf WE. Steroid hormones and the cardiovascular system: direct actions of estradiol, progesterone, testosterone, gluco- and mineralcorticoids, and soltriol [vitamin D] on central nervous regulatory and peripheral tissues. *Experientia*. 1990;46:13–25. DOI: 10.1007/BF01955408.
2. Sedlak T, Shufelt C, Iribarren C, Merz CN. Sex hormones and the QT interval: a review. *J Womens Health (Larchmt)*. 2012;21:933–941. DOI: 10.1089/jwh.2011.3444.
3. Kuiri-Hänninen T, Sankilampi U, Dunkel L. Activation of the hypothalamic-pituitary-gonadal axis in infancy: minipuberty. *Horm Res Paediatr*. 2014;82:73–80. DOI: 10.1159/000362414.
4. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men: Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab*. 2001;86:724–731. DOI: 10.1210/jcem.86.2.7219.
5. Abehsira G, Bachelot A, Badilini F, Koehl L, Lebot M, Favet C, Touraine P, Funck-Brentano C, Salem JE. Complex influence of gonadotropins and sex steroid hormones on QT interval duration. *J Clin Endocrinol Metab*. 2016;101:2776–2784. DOI: 10.1210/jc.2016-1877.
6. Kirilmaz A, Bolu E, Kilicaslan F, Erinc K, Uzun M, Isik E, Ozata M, Ozdemir C, Demirtas E. Comparison of electrocardiographic repolarization patterns between hypogonad males and normal subjects. *Ann Noninvasive Electrocardiol*. 2003;8:284–288. DOI: 10.1046/j.1542-474X.2003.08404.x.
7. Bidoggia H, Maciel JP, Capalozza N, Mosca S, Blaksley EJ, Valverde E, Bertran G, Arini P, Biagetti MO, Quinteiro RA. Sex differences on the electrocardiographic pattern of cardiac repolarization: possible role of testosterone. *Am Heart J*. 2000;140:678–683. DOI: 10.1067/mhj.2000.109918.
8. Schwartz PJ, Ackerman MJ. The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy. *Eur Heart J*. 2013;34:3109–3116. DOI: 10.1093/eurheartj/eht089.
9. Vink AS, Clur SB, Wilde AAM, Blom NA. Effect of age and gender on the QTc-interval in healthy individuals and patients with long-QT syndrome. *Trends Cardiovasc Med*. 2018;28:64–75. DOI: 10.1016/j.tcm.2017.07.012.
10. Buber J, Mathew J, Moss AJ, Hall WJ, Barsheshet A, McNitt S, Robinson JL, Zareba W, Ackerman MJ, Kaufman ES, et al. Risk of recurrent cardiac events after onset of menopause in women with congenital long-QT syndrome types 1 and 2. *Circulation*. 2011;123:2784–2791. DOI: 10.1161/CIRCULATIONAHA.110.000620.
11. Rashba EJ, Zareba W, Moss AJ, Hall WJ, Robinson J, Locati EH, Schwartz PJ, Andrews M; LQTS Investigators. Influence of pregnancy on the risk for cardiac events in patients with hereditary long QT syndrome. *Circulation*. 1998;97:451–456. DOI: 10.1161/01.CIR.97.5.451.
12. Seth R, Moss AJ, McNitt S, Zareba W, Andrews ML, Qi M, Robinson JL, Goldenberg I, Ackerman MJ, Benhorin J, et al. Long QT syndrome and pregnancy. *J Am Coll Cardiol*. 2007;49:1092–1098. DOI: 10.1016/j.jacc.2006.09.054.
13. Hasegawa K, Ito H, Kaseno K, Miyazaki S, Shiomi Y, Tama N, Ikeda H, Ishida K, Uzui H, Ohno S, et al. Impact of medical castration on malignant arrhythmias in patients with prostate cancer. *J Am Heart Assoc*. 2021;10:e017267. DOI: 10.1161/JAHA.120.017267.
14. Salem JE, Bretagne M, Lebrun-Vignes B, Waintraub X, Gandjbakhch E, Hidden-Lucet F, Gougis P, Bachelot A, Funck-Brentano C. Clinical characterization of men with long QT syndrome and torsades de pointes associated with hypogonadism: a review and pharmacovigilance study. *Arch Cardiovasc Dis*. 2019;112:699–712. DOI: 10.1016/j.acvd.2019.06.008.
15. Chorin E, Havakuk O, Adler A, Steinvil A, Rozovski U, van der Werf C, Postema PG, Topaz G, Wilde AAM, Viskin S, et al. Diagnostic value of T-wave morphology changes during "QT stretching" in patients with long QT syndrome. *Heart Rhythm*. 2015;12:2263–2271. DOI: 10.1016/j.hrthm.2015.06.040.
16. Postema PG, Ritsema van Eck HJ, Opthof T, van Herpen G, van Dessel PF, Priori SG, Wolpert C, Borggrefe M, Kors JA, Wilde AA. IK1 modulates the U-wave: insights in a 100 year old enigma. *Heart Rhythm*. 2009;6:393–400. DOI: 10.1016/j.hrthm.2008.11.024.
17. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, Philippides GJ, Roden DM, Zareba W. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*. 2010;121:1047–1060. DOI: 10.1161/CIRCULATIONAHA.109.192704.
18. Kolder ICRM, Tanck MWT, Postema PG, Barc J, Sinner MF, Zumhagen S, Husemann A, Stallmeyer B, Koopmann TT, Hofman N, et al. Analysis for genetic modifiers of disease severity in patients with long QT syndrome type 2. *Circ Cardiovasc Genet*. 2015;8:447–456. DOI: 10.1161/CIRCGENETICS.114.000785.
19. Matsuo K, Akahoshi M, Seto S, Yano K. Disappearance of the Brugada-type electrocardiogram after surgical castration: a role for testosterone and an explanation for the male preponderance. *Pacing Clin Electrophysiol*. 2003;26:1551–1553. DOI: 10.1046/j.1460-9592.2003.t01-1-00227.x.
20. Shimizu W, Matsuo K, Kokubo Y, Satomi K, Kurita T, Noda T, Nagaya N, Suyama K, Aihara N, Kamakura S, et al. Sex hormone and gender difference–role of testosterone on male predominance in Brugada syndrome. *J Cardiovasc Electrophysiol*. 2007;18:415–421. DOI: 10.1111/j.1540-8167.2006.00743.x.