EDITORIAL

Modulating Effects of Sex Hormones on Cardiac Function

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Gender differences in cardiac function, especially heart rate, were noted even before Hippocrates. Women have a faster resting heart rate than men, and the heart rate is known to vary during the menstrual cycle. Following the introduction of the electrocardiogram, it was appreciated early on that the QRS duration is longer in adult males than females, most probably as a result of increased myocardial muscle mass in men. Bazett and Fridericia recognized that the duration of ventricular repolarization, corrected for heart rate, was longer in women than men. Subsequently, it was appreciated that the QT interval and heart rate were similar in young boys and girls, and that the change in heart rate and QT interval began during adolescence with the heart rate slowing and QT interval shortening in males as they progressed through puberty.¹ More recently, it was realized that autonomic tone and modulation of beat-to-beat variability in heart rate, i.e., heart rate variability, was quite different between the sexes.²

In addition to gender-related changes in cardiac function, it was appreciated almost from the beginning of time that men and women had different susceptibilities to cardiac disease. Women seemed relatively resistant to coronary disease before menopause, with the rate of coronary disease rapidly increasing after menopause. These observations led to clinical trials in which adult males with coronary disease were prescribed estrogens in hopes of inhibiting the progression of coronary atherosclerosis. These trials were stopped early because of increased event rates among men receiving estrogens as compared with those receiving placebo.

The distribution of cardiac events is different in several genetic disorders with autosomal dominant

(nonsex related) inheritance. For example, in the long QT syndrome, women after adolescence have a higher frequency of arrhythmogenic syncope and cardiac arrest than men.³ In the Brugada syndrome, men having more marked ST-segment elevations in the precordial leads are more vulnerable to life-threatening arrhythmias than women.⁴

Arrhythmogenic susceptibility also seems to be different by gender. Women seem to have a lower rate of experiencing the Wolf-Parkinson-White syndrome and atrial fibrillation, but a higher rate of atrioventricular nodal tachycardia. Women are unusually susceptible to the QT prolonging effects of drugs,⁵ possibly because the underlying QT interval is longer in women than men.

All these examples highlight the complex interplay of sex hormones on the heart. It is now appreciated that estrogen and testosterone receptors are present in the heart, and these hormones can modulate ion-channel currents. It is quite obvious that the sex genotypes provide different phenotypic internal environments in women and men, and these differences will be manifest in gender-related differences in cardiac structure, function, and susceptibility to disease.

This issue of *Annals* includes three gender-related articles that touch on various aspects of the influence of sex hormones on cardiac function. Saba et al. investigated the effects of estrogen on autonomic inputs into the sinus and atrioventricular nodes in mice during ambulatory monitoring.⁶ Although we do not usually publish animal investigations in *Annals*, this article provides new insights into basic electrophysiologic phenomena. Wranicz et al. examined the relationship between testosterone and estradiol concentrations and heart rate variability in men after myocardial infarction.⁷ It appears that testosterone promotes

parasympathetic dominance. In the third article, Endres et al. studied the effects of three phases of the menstrual cycle after autonomic blockade on early (ST-segment height) and late (QT_c variation) aspects of repolarization.⁸ Their data suggest that female sex hormones modulate ventricular repolarization.

One does not need sophisticated laboratory studies to determine the sex genotype. Noninvasive electrophysiology is well positioned to explore the phenotypic differences and the mechanisms modulating gender-related genetic differences in cardiac function.

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