Gender Differences in Idiopathic Ventricular Arrhythmias – Understanding a Woman’s Heart –
Akihiko Nogami, MD

Sustained monomorphic ventricular tachycardia (VT) is most often related to myocardial structural heart disease, including a healed myocardial infarction, and cardiomyopathies. However, no apparent structural abnormalities are identified in approximately 10% of all cases of sustained monomorphic VT in the United States and in 20% of those in Japan. These cases of VT are referred to as “idiopathic”. Idiopathic VTs usually occur in specific locations of the heart and have specific QRS morphologies, whereas VTs associated with structural heart disease have a QRS morphology that tends to indicate the location of the scar. Idiopathic VT comprises multiple, discrete subtypes that are best differentiated by their mechanism, QRS morphology, and site of origin. The predominant site of origin for idiopathic right VT is the right ventricular outflow tract (RVOT), and the tricuspid annulus VT is the second most common idiopathic right-sided VT. In idiopathic left-sided VTs, there are Purkinje-related VTs, mitral annular VTs, and left ventricular outflow tract (LVOT) VTs. According to the mechanism, idiopathic VT has been classified into 3 subgroups: a verapamil-sensitive type (reentry), adenosine-sensitive type (triggered activity), and propranolol-sensitive type (automaticity). Although the mechanism of RVOT-VT is mainly triggered activity and that of verapamil-sensitive left fascicular VT is reentry, the mechanisms of the other idiopathic VTs are not homogeneous.

Article p1585

The article by Tanaka et al in this issue of the Journal contributes to the differentiation of the various forms of idiopathic VT and ventricular premature beats (VPBs) by showing that gender and age differences exist among them. The authors analyzed data from their patients with drug-resistant idiopathic ventricular arrhythmias (VAs: VT or VPB), and concluded that RVOT-VAs in women were 1.5-fold more frequent than in men, whereas LVOT-VAs were more frequent in men. They also demonstrated that the prevalence of LVOT-VAs increased with age compared with that for RVOT.

Gender difference in incidence has been reported for various types of arrhythmias. The first observation of a gender difference in the ECG was published 90 years ago by Bazett, who demonstrated that women had significantly longer QT intervals than men, despite having higher heart rates. However, the differences in autonomic tone and menstrual cycle variability in the corrected QT in women at rest do not appear to be responsible for the gender differences in the QT interval. In a review of gender differences in cardiac repolarization, James et al provided an extensive discussion of the experimental data and potential gender differences in ionic currents at the cellular level and the possible roles played by sex hormones in some of the better-characterized gender differences in cardiac repolarization. Women with the LQT1 and LQT2 variants of congenital long-QT syndrome (LQTS) are at greater risk of adverse cardiac events. Similarly, many drugs associated with acquired LQTS have a greater risk of inducing torsades de pointes (TdP) type arrhythmias in women than in men.

In contrast, men show a higher incidence of atrial fibrillation, Brugada syndrome (BS), early repolarization syndrome (ERS), and sudden death compared with women. Women with BS have a lower prevalence of life-threatening arrhythmias compared with men. The basis for this intriguing gender-related difference in disease penetration is not completely understood. It seems that a more prominent in the RV epicardium in men contributes to their predisposition to develop the BS phenotype. However, hormonal, environmental, or genetic factors other than the SCN5A mutation may alter the function of the gene, or of other yet unknown factors, would explain the gender difference in disease penetrance. There are also gender differences in ERS. Among survivors of idiopathic ventricular fibrillation (VF), those with ER were more likely to be men than those without ER. J-point elevation is sometimes observed in control subjects, especially young athletes. Healthy male subjects show J-point elevation more often than female subjects.

Nakagawa et al analyzed the data from patients with idiopathic VT in their review of peer-reviewed publications. They concluded that in idiopathic VT arising from the RVOT there was a 2:1 female predominance, whereas in verapamil-sensitive fascicular VT there was a 3:1 male predominance. Their data regarding LVOT-VT were not conclusive because of the small number of reported patients with LVOT-VT. Of interest, in this issue of the Journal, Tanaka et al demonstrate that LVOT-VAs are more frequent in men and that the prevalence of LVOT-VAs increases with age. In general, RVOT-VAs are adrenergically mediated and sensitive to decreased intracellular calcium. Iwai et al further indicated that the electrophysiologic and pharmacologic properties, which include sensitivity to adenosine, are similar for RVOT and LVOT arrhythmias and they hypothesized a common arrhythmogenic mechanism, consistent with cyclic AMP-mediated trig.
tered activity, despite disparate sites of origin. Philp et al. showed that 17-β-estradiol can exert an antiarrhythmic effect by inhibiting the Ca\textsuperscript{2+} channel, which indicates that a reduction in the 17-β-estradiol level may exert a proarrhythmic effect, which could lead to activation of the Ca\textsuperscript{2+} channels. However, this evidence for a common electrophysiologic mechanism of LVOT-VT, especially that with an epicardial origin that could be ablated from the aortic sinus cusp. The increased prevalence of LVOT-VAs with age also suggests that increased myocardial fibrosis in the older population results in slower conduction.

Finally, an important consideration is the “malignant” subtype of RVOT-VAs. Idiopathic VAs from the RVOT are usually considered “benign”, because those VAs are mostly hemodynamically stable. However, idiopathic polymorphic VT or VF is sometimes triggered by VPBs arising from the RVOT. Noda et al. reported 16 patients without any structural heart disease who had VF or polymorphic VT that was initiated by VPBs from the RVOT. Among those patients, 9 (56%) were women. Further, among 5 patients with VF, 4 (80%) were women. In my own experience, among 14 patients with VF or polymorphic VT that was triggered by VPB from the RVOT, 12 (86%) were women, and among 73 patients with monomorphic RVOT-VT, 44 (60%) were women (unpublished data). This higher prevalence of “malignant” VPBs from the RVOT in women may be related to gender differences in repolarization. Further investigation is needed to identify the mechanism of the gender differences in the site of VA origin and thus risk stratification.

References