Female gender: risk factor for congenital long QT-related arrhythmias
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Congenital long-QT syndrome (LQTS) is a genetic cardiac channelopathy in which patients exhibit delayed ventricular repolarization that appears as a prolongation of the corrected QT (QTc) interval on the electrocardiogram. More than 200 mutations have been found in 13 different genes encoding ion channels, accessory beta subunits, and regulatory proteins. Most cases of congenital LQTS are the consequence of the dominant inheritance of a given mutation. Kv11.1 mutations are the most frequent ones (45%), followed by those found in Kv7.1 (42%), Nav1.5 (8%), KCNE1 (3%), and KCNE2 (2%). In addition, another type of LQTS, the ‘acquired’ LQTS, has been described, mostly as the consequence of drugs able to prolong the cardiac action potential duration. This lengthening of the cardiac action potential can produce the development of early afterdepolarizations (EADs) and the genesis of a ventricular polymorphic arrhythmia called torsades de pointes (TdP) that, in turn, can result in recurrent spontaneous syncope, seizures, and sometimes sudden cardiac death.

The cardiac sodium channel (Nav1.5) is a member of the voltage-dependent family of sodium channels that consist of heteromeric assemblies of the pore-forming alpha subunit. The activation of Nav1.5 channels produces a massive influx of sodium ions into the cytoplasm and, thus, the depolarization of the membrane potential of cardiac cells within tenths of milliseconds, playing a crucial role in the genesis of cardiac action potentials and in the conduction velocity. Nav1.5 channels inactivate at the end of the upstroke of the action potential and can only reactivate after the membrane potential becomes negative during the phase 4. However, a certain proportion of sodium channels remain active during the plateau phase due to their ability to reopen. This activity generates a small inward sodium current, the so-called late \( I_{Na} \) or \( I_{Na,L} \), and a gain of function of \( I_{Na,L} \) represents the underlying mechanism of LQTS3.

Epidemiological risk factors such as sex, electrolyte imbalance, ischaemia, and QT-prolonging drugs have been well established. In fact, female compared with male sex is associated with a two- to three-fold increased frequency of TdP. Under basal conditions, men exhibit shorter cardiac action potentials and, thus, a shorter QTc interval. These protective effects for LQTS have been correlated with testosterone levels as well as the effects of gonadal steroids on ion channels and their genomic effects (e.g. the influence on the ion channel expression). Testosterone decreases dofetilide-induced proarrhythmia in female rabbits, and this effect can be due to its actions on ion channels (it decreases \( I_{Ca,L} \), enhances \( I_{Ks} \) and \( I_{K1} \) and has no effect on \( I_{Kr} \) currents). On the other hand, progesterone slightly shortens the action potential duration (APD) under basal conditions, although it lengthens APD after mimicking the sympathetic nervous system stimulation (e.g. by adding cAMP to the internal solution in the patch pipette) mostly through inhibition of \( I_{Ca,L} \) and enhancement of the \( I_{Ks} \). Finally, oestrogens increase the cardiac.
In the present issue of this journal, Lowe et al. studied whether the gender-dependent function of late INa post-depolarization contributes to the arrhythmia susceptibility. The study was conducted in male and female mice in which the canonical cardiac sodium channel SCN5A locus was disrupted, and the expression of human wild-type SCN5A cDNA substituted. The authors induced the appearance of TdP by activating Nav1.5 channels after exposure of the animals to anemone toxin II (ATX-II), thus mimicking LQTS3. Most female mice treated with ATX-II elicited polymorphic ventricular tachycardia, whereas none of the male mice elicited this arrhythmia under the same experimental conditions. These effects could not be attributed to different levels of expression of the channels, since the levels of expression of Nav1.5 were similar in males and females. This is the first study which reports that the augmentation of the already larger late current in female mice results in longer action potentials as well as the generation of EADs, particularly at slow frequencies of stimulation. Therefore, this study represents the first evidence of a gender-dependent disruption in repolarization due to an increase in the magnitude of the INa-L.

Surprisingly, ranolazine did not differentially affect the cardiac action potential duration recorded in males or females. These effects can be due to the fact that the experiments were performed in mice and repolarization in this animal species is different from that of humans. Moreover, Nav1.5 channels interact with a plethora of proteins that can affect their function. Thus, further studies focusing on the gender differences in the late sodium current with or without these modulator proteins are necessary to better understand the mechanisms involved in gender differences.