Sex, Calcium and Arrhythmias

Women have a longer baseline QTc than men, and are at higher risk (60-75%) for long QT syndrome (LQTS) than men. LQTS is characterized by sudden syncopal attacks, seizures, and sudden death. LQTS is associated with a form of polymorphic ventricular tachycardia, called Torsade de Pointes (TdP) which often leads to sudden death and remains a major health problem.

TdP caused by the suppression of the fast component of the delayed rectifying K+ current, I_{Kr} results in repolarization delay and QT prolongation, called Long QT type 2 (LQT2). Sex differences in the propensity to LQT2 have been attributed to a reduced ‘repolarization reserve’ in females and is observed in other mammalian hearts (rabbits, dogs and guinea pigs). Recent studies from our group has discovered that in rabbit hearts, estrogen (0.3-1nM) upregulates voltage-gated L-type Ca^{2+} channels and Na/Ca exchanger (NCX) to increase their currents, I_{Ca,L} and I_{NCX} selectively at the base of the heart. Estrogen acts via a genomic mechanism (in 24-48 hrs) to increase levels of message, protein and current densities. Repolarization delay prolongs the action potential, changes the balance of Ca^{2+} influx vs. efflux leading to sarcoplasmic reticulum (SR) Ca^{2+} overload. In minutes, SR overload produces cell-synchronous systolic secondary Ca^{2+} elevations (SSCEs) in local islands of epicardium. SSCEs precede voltage depolarization during the AP-plateau and cause the re-activation of L-type Ca^{2+} channels, ectopic beats and TdP. Parallels between rabbit model of drug-induced LQT2 and human tissues will be discussed.
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