ΔKPQ mutation in LQT3 results in increased frequency and stability of reentry

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Max 1950 chars

The ΔKPQ is a mutation in the SCN5A gene that encodes the α-subunit of the Na^+ channel and leads to one of the most severe forms of the long-QT syndrome (LQT3). It may result in syncope and sudden cardiac death. ΔKPQ disrupts the fast inactivation of the channel and leads to a residual depolarizing Na^+ current that prolongs the duration of the action potential and may induce early after-depolarizations (EADs). However, the consequences of the ΔKPQ mutation on impulse propagation and reentry have never been studied. We incorporated the Clancy-Rudy Markovian formalism of the Na^+ channel into a Luo-Rudy dynamic cardiac cell model whose activity was integrated over time in 1-dimensional (1D, 2 cm) and 2-dimensional (2D, 2 x 2 cm) models. Penetrance of the ΔKPQ mutation was simulated by changing the percentage of channels having the mutation in each cell. The 1D strand was paced at a cycle length of 1 sec. In the 2D strands, reentry was initiated by cross-field stimulation and simulated under conditions of 0, 25, 50, 75 and 100% penetrance. Simulations in the 1D strand predicted a steady state conduction velocity of ~48 cm/sec regardless of penetrance. However, the 2D sheet containing mutant cells displayed varying dynamics and frequency of reentry, depending on penetrance. In general, the higher the penetrance the higher the stability and frequency of the rotor and the smaller the core size. In addition, a clustering of frequencies was observed whereby, at 0 and 25% penetrance, the wavefront rotated at 8.2-8.5 Hz, whereas between 50 and 100% penetrance the wavefront rotated at 9.5-9.9 Hz. These results suggest that while the ΔKPQ mutation need not affect conduction velocity of a plane wave, during reentry the sink (repolarizing) effects exerted by the reentry core abbreviate prematurely the action potential duration of cells in its immediate surroundings and allow the excessive sodium channel availability to accelerate and stabilize the rotor. These results add to the understanding of the mechanisms underlying the higher risk of LQT3 patients to sudden cardiac death.