

Optimization of a Cardiomyocyte Model Illuminates Role of Increased INaL in Repolarization Reserve

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Cardiac ion channels compensate for each other when one is compromised by a congenital or drug-induced defect. Such redundancy contributes to a robust repolarization reserve that can prevent the development of lethal arrhythmias. Most efforts made to describe this phenomenon have quantified effects by individual ion channels. Since arrhythmia mitigation is dependent on the state of all cardiac ion channels, research using a systems-level approach is important. However, the interplay between all major ion channels, and the mechanism to which their redundancy can increase repolarization reserve, has yet to be studied. Here a genetic algorithm was designed to derive a profile that optimizes repolarization reserve.

The algorithm first generated a random population of profiles, which contain key ion-channel conductances scaled between 33-300% of their baseline values. The Tomek et al. (ToR-ORd) model was then used for simulations to ensure that each produced physiologic morphology. Repolarization reserve was quantified using a previously defined metric, repolarization reserve current (RRC), i.e., the minimum constant current to prevent normal action potential (AP) repolarization in a cell. Low RRC values were penalized as it indicates reduced repolarization reserve.

The resulting profile generated an optimized ToR-ORd model that increased RRC by 80% compared to baseline. It also uncovered previously unreported behavior by the late sodium current (INaL). Simulations demonstrated that INaL increased AP duration, without compromising RRC. This was further validated in the Grandi et al model, which has a reduced baseline RRC and does not include INaL. A physiologic AP with a significantly increased RRC was obtained after adding INaL.

This work defines the first ion-channel conductance profile for increased RRC. Additionally, the unbiased computational approach illuminated mechanistic insights to how the metric could be increased. Ultimately, this study broadens our understanding of repolarization reserve, which may allow for the improvement of arrhythmia mitigation strategies.