OFFICIAL ABSTRACT and CERTIFICATION

The Role of Delayed Rectifier Potassium Currents in Human Ventricular Cardiomyocyte Arrhythmogenesis

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Cardiac arrhythmias are among one of the most widely recognized medical conditions, with the ability to both diminish quality of life and trigger cardiac arrest. Cellular irregularities that can cause arrhythmias have been identified but the mechanisms behind these events are difficult to study in vitro and in vivo due to the complexity of cardiomyocytes. This study will attempt to determine the effect of two ionic currents, the rapid and slow delayed rectifier potassium currents IKr and IKs, in generating arrhythmogenic behavior in the O ' Hara-Rudy (ORd) model of a human ventricular cardiomyocyte. As demonstrated in the Livshitz-Rudy (LivR) guinea pig ventricular cardiomyocyte model, a hypothesized IKs feedback loop rendered that a higher concentration of IKs was increasingly beneficial to cellular stability. However, differences in guinea pig ventricular cardiomyocytes imply that while the same feedback loop may hold true in humans, the effects will be relatively smaller. Parameter sensitivity analysis of the LivR model and ORd model reveal variation in IKs channels, sodium dynamics, and calcium sensitivity. Further exploration of the ORd model determined that it was advantageous to modify the model before formal experimentation. Original C++ code was integrated into the ORd model to indicate the presence of arrhythmogenic behavior. The results suggested that a greater concentration of IKs provided a higher resistance to arrhythmogenic behavior, up to a ratio of 7/1 : IKs/IKr. This seminal initial study opens the possibility of exploring novel targets for antiarrhythmic drugs and determining the existence of ideal ratios of each current to discourage cellular arrhythmogenesis in extreme environments. Both offer exciting promises to the future of treating cardiac arrhythmias.

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