Analysis and Improvement of a Human Ventricular Cell Model for Investigation of Cardiac Arrhythmias

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Background: Mathematical modeling and simulation of hearts electrical activity has become a fundamental tool to understand cardiac behavior. Different models have been proposed, each one aimed at investigating specific questions. A human ventricular action potential (AP) model was recently proposed by Grandi et al (2010). In this study we have conducted a thorough evaluation of that model, and we have proposed several improvements that render it suitable for cardiac arrhythmia investigations.

Methods: Four stimulation protocols were applied to the original and improved models, and a number of cellular arrhythmic risk biomarkers were computed, including: steady-state AP and [Ca2+] transient properties, AP duration (APD) restitution curves, APD adaptation to abrupt changes in heart rate, and intracellular [Ca2+] and [Na+] rate dependence.

Results: In its original version the Grandi model proved to adequately reproduce AP triangulation (APD90-APD50=59.3ms), and maximum normalized systolic [Ca2+] and [Na+] levels (180% and 132%), outperforming other previous models. However, APD rate adaptation did not show the biphasic behavior (with characteristic fast and slow adaptation phases), and the maximum slope of the S1S2 restitution curve was out of physiological range (S_S1S2=10.18). Based on those results, we reformulated the L-type calcium current (ICaL) to include both fast and slow voltage-dependent inactivation gates, we updated the inward rectifier K+ current (IK1) based on recent experimental data, we shifted the voltage-dependence curve of the Na+ current inactivation gates, and we adjusted the conductance of the slow delayed rectifier K+ current (IKs) and maximal value of the Na+/K+ pump. Our modifications led to: a) further improved AP triangulation (64.7ms); b) APD rate adaptation curves characterized by fast and slow time constants within physiological ranges (8.92s and 84.21s); c) S1S2 restitution slope in accordance with experimental data (S_S1S2=1.6).

Conclusions: An improved human ventricular cell model has been developed and validated for cardiac arrhythmia investigations.