Computational Modeling of Inherited Arrhythmogenic Disorders of the Heart for Targeted Pharmacotherapy: Introducing an Emerging Cardiac Electrophysiology Research Tool

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Computational modeling of human diseases is an emerging field of research interests.1-4 The methodology applied is absolutely non-invasive, producing no harm to the patient or animals, and information so obtained is useful for identifying and/or confirming the underlying pathogenetic mechanism.

In this communication, we describe how modeling can recapitulate clinical features of inherited arrhythmogenic disorders of the heart. Taking Timothy syndrome (TS), a malignant form of long QT syndrome referred to as LQT8, in which patients seldom survive beyond three years of age, as an example, modeling was intended to define the mechanism by which recurrent ventricular tachyarrhythmias could be provoked by enhanced sympathetic tone (e.g., exertion and/or emotional distress) and to search for potential targeted sites for pharmacotherapy beyond beta-adrenergic blockers which clinically often fail to provide complete protection.5

The study used the latest state-of-the-art Luo-Rudy guinea pig ventricular myocyte model,1-3,6 which is formulated with various ion channels based on the Hodgkin-Huxley theme and is also incorporated with interacting structure-based Markov models (gating mechanisms) of the L-type Ca2+ channel (ICa,L) and ryanodine receptor (RyR2). The Markov model of the ICa,L channel has a conducting mode (ModeV) and a non-conducting mode (ModeCa). ModeV contains four closed states, a single conducting state, an inactivation state into which channels move fast (IVf) following depolarization and another inactivation state into which channels move slowly (IVs). ModeCa represents channels that are inactivated due to Ca2+. Additionally, channels can also move into another non-conducting Mode0 as channels are activated in the presence of isoproterenol. Transitions among these states are affected by changes in voltage and Ca2+ concentrations. The ICa,L channel interacts with the Markov model of ryanodine receptor (RyR2) in restricted t-tubular subsarcolemal space for Ca2+ distribution. Intracellular Ca2+ cycling processes include Ca2+ uptake and release by SR and a buffering system (e.g., calmodulin, troponin, and calsequestrin).

We simulated various clinical scenarios of TS with stepwise increase in the percentage of G406R-mutated Cav1.2 channels, which have been shown to suppress voltage-dependent inactivation of the channel, from 0 to 11.5 and 23%, and to 38.5 and 77%, respectively, for heterozygous and homozygous states of TS1 and TS2.5 Progressive prolongation of action potential duration (APD) and QT interval accompanied by amplification of transmural dispersion of repolarization (TDR) (Figure 1), steepening of APD restitution, induction of delayed afterdepolarizations (DADs) and both DAD- and phase-3-early-afterdepolarization-mediated triggered activities correlated well with the extent of G406R Cav1.2 channel mutation. BAS amplified TDR, steepened APD restitution and facilitated the inducibility of DAD-mediated triggered activity. Systematic analysis of intracellular...
Ca\(^{2+}\) cycling revealed that SR Ca\(^{2+}\) ATPase (I\(_{\text{UP}}\)) played an essential role in BAS-induced facilitation of DAD-mediated triggered activity (Figure 2) and, in addition to I\(_{\text{Ca,L}}\), it was essential for the facilitation of arrhythmogenesis under the influence of BAS. Thus, G406R Ca\(_{1.2}\) channel mutation confers not only a trigger but also a substrate for the development of ventricular arrhythmias which can be exaggerated by BAS. We concluded that, besides beta-adrenergic blockers and I\(_{\text{Ca,L}}\) channel blockers, an agent aimed at reduction of I\(_{\text{UP}}\) may additionally provide antiarrhythmic efficacy in patients with TS (Figure 3).

Similarly, we are currently applying this modeling method for other inherited arrhythmogenic disorders with adrenergically mediated ventricular arrhythmias such as Andersen-Tawil syndrome (LQT7)\(^7\) and catecholaminergic polymorphic ventricular tachycardia. Preliminary results suggest that, depending on the underlying mechanism, the effective targeted site of antiarrhythmic therapy beyond beta-adrenergic receptors varies somewhat among these different forms of inherited arrhythmogenic disorders.

We anticipate that the technique of computational modeling will be an integral part of translational research, providing direction for basic and clinical investigations. However, further refinement of the modeling methodology is required so as to enhance its predictive power.\(^8\)
REFERENCES


