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Electrophysiological properties of computational human ventricular cell action potential models under acute ischemic conditions

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ABSTRACT

Acute myocardial ischemia is one of the main causes of sudden cardiac death. The mechanisms have been investigated primarily in experimental and computational studies using different animal species, but human studies remain scarce. In this study, we assess the ability of four human ventricular action potential models (ten Tusscher and Panfilov, 2006; Grandi et al., 2010; Carro et al., 2011; O'Hara et al., 2011) to simulate key electrophysiological consequences of acute myocardial ischemia in single cell and tissue simulations. We specifically focus on evaluating the effect of extracellular potassium concentration and activation of the ATP-sensitive inward-rectifying potassium current on action potential duration, post-repolarization refractoriness, and conduction velocity, as the most critical factors in determining reentry vulnerability during ischemia. Our results show that the Grandi and O'Hara models required modifications to reproduce expected ischemic changes, specifically modifying the intracellular potassium concentration in the Grandi model and the sodium current in the O'Hara model. With these modifications, the four human ventricular cell AP models analyzed in this study reproduce the electrophysiological alterations in repolarization, refractoriness, and conduction velocity caused by acute myocardial ischemia. However, quantitative differences are observed between the models and overall, the ten Tusscher and modified O'Hara models show closest agreement to experimental data.

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1. Introduction

One of the major causes of sudden cardiac death is acute myocardial ischemia, resulting from an imbalance in the supply and demand of oxygen and nutrients to the heart. During the first 10–15 min of ischemia, metabolic and electrophysiological changes occur rapidly and vary spatially, resulting in a shortening of action potential duration (APD), a prolongation of effective refractory period (ERP) beyond APD (termed post-repolarization refractoriness, PRR), and a reduction of AP upstroke and conduction velocity (CV) compared to normal tissue (Sutton et al., 2000; Taggart, 2000). The resulting electrophysiological heterogeneities between normal and ischemic tissue provide the substrate for reentrant arrhythmias, as demonstrated in experimental and simulation studies (Dutta et al., 2016; Janse and Wit, 1989; Pogwizd and Corr, 1987; Tice et al., 2007). Previous research has shown that these changes are mainly caused by: hyperkalemia (increased extracellular potassium concentration, $[K^+]_o$) (Pandit et al., 2010; Schaapherder et al., 1990), which results in an increase in cell resting membrane potential and decreased cell excitability; hypoxia (inadequate supply of oxygen) (Van Wagoner and Lamorgese, 1994; Weiss et al., 1992), which results in an opening of ATP-sensitive inward-rectifying potassium current ($I_{K(ATP)}$) channels; and acidosis (reduced intracellular pH) (Sato et al., 1985; Yatani et al., 1984), which decreases the conductance of the sodium (I_{Na}) and L-type calcium (I_{CaL}) currents (Carmeliet, 1999). However, ischemia is a complex and dynamic process, which needs to be further investigated for a better understanding of ischemia-induced arrhythmia mechanisms.

Most research on ischemia has been carried out in animals (Carmeliet, 1999; Coronel et al., 1988; Fiolet et al., 1985; Furukawa et al., 1991; Ma and Wang, 2007; Pandit et al., 2011; Schaapherder et al., 1990; Wilensky et al., 1986), and data from human is scarce (Sutton et al., 2000; Taggart, 2000). Therefore, extrapolation of mechanisms from animal to human is challenging, but can be facilitated by computational modeling using multi-scale human-specific models (Rodriguez et al., 2016). These computational models provide a flexible platform to impose specific changes not possible in experimental studies and dissect mechanisms with high spatio-temporal resolution, to increase our understanding of ischemia-induced arrhythmic mechanisms in human. Most human models, however, have been created and evaluated using data from healthy cells and their applicability for simulations of ischemia is currently unknown. Therefore, it is important to assess their behavior under varied ischemic conditions, as the ischemic changes described above vary through time and space in and around the ischemic area (Coronel et al., 1988; Fiolet et al., 1985; Schaapherder et al., 1990; Wilensky et al., 1986). Furthermore, even species-specific (e.g., human) models are based on experimental data acquired from different species (e.g., rabbit, pig, etc.) (Niederer et al., 2009); a comparison and assessment between the different model outputs and to experimental data is thus necessary, especially under varying conditions such as ischemia, as has been done in previous studies (Cherry and Fenton, 2007; Gemmell et al., 2016; O'Hara and Rudy, 2012; ten Tusscher et al., 2006).

The aim of this study is to investigate the response of the four most recent computational human-specific ventricular action potential (AP) models (the ten Tusscher and Panfilov, 2006; Grandi et al., 2010; Carro et al., 2011; O'Hara et al. 2011 models) to varied ischemic conditions by comparing electrophysiological properties in single cell and tissue simulations in order to assess their utility for studying mechanisms of arrhythmogenesis during the initial phase of acute myocardial ischemia.

2. Methods

2.1. Human ventricular cell models

Four human ventricular models were investigated in this study: the ten Tusscher et al., the Grandi et al., the Carro et al., and the O'Hara et al. models (Carro et al., 2011; Grandi et al., 2010; O'Hara et al., 2011; ten Tusscher and Panfilov, 2006); a detailed description of the models can be found in the original publications. The ten Tusscher et al. (TP06) model is the most widely used and studied human model, it is based on a previous human model from the same group (ten Tusscher et al., 2004). However, the model does not adequately reproduce AP response to frequency changes and block of potassium currents. The Grandi et al. model (GPB), based on a previously developed rabbit cell model (Shannon et al., 2004), overcomes limitations of the TP06 model. However, based on an analysis of GPB APD restitution and rate adaptation shortcomings, Carro et al. (CRLP) modified and reformulated various currents, including I_{CaL} and the inward rectifying potassium current, I_{K1}; although the CRLP calcium dynamics still needs further improvement compared to the TP06 calcium dynamics. Finally, the most recent human cell model is the O'Hara et al., 2011 model (ORd) (O'Hara et al., 2011), based on human data obtained from over 100 undiseased human hearts. Most notably, the model incorporates the effects of Ca^{2+}/calmodulin-dependent protein kinase II (CaMK) on known ionic currents. Nonetheless, the model is limited in simulating hyperkalemia in tissue, as the model does not reproduce propagation of excitation for $[K^+]_o \geq 6$ mM; an issue that we address in this study.

2.2. Ischemic electrophysiological changes

The $I_{K(ATP)}$ current: $I_{K(ATP)} = G_{K(ATP)} f_{K(ATP)} \left(\frac{[K^+]_o}{[K^+]_{o,n}}\right)^{0.24} (V_m - E_K)$, was based on a previous formulations (Ferrero et al., 1996; Michailova et al., 2007; Shaw and Rudy, 1997) and added to the cell models using COR (Garny et al., 2003). The amplitude of the current depends on the ratio of the present $[K^+]_o$, and the control value of $[K^+]_o$ ($[K^+]_{o,n}$). It also depends on the membrane potential of the cell, V_m, and the Nernst potential of potassium, E_K. We used the value estimated by Michailova et al. (2007). for the channel conductance ($G_{K(ATP)} = 0.05$ mS/μF) and used $f_{K(ATP)}$ as a scaling factor to vary peak $I_{K(ATP)}$ conductance in the models.

We simulated the electrophysiological consequences of the