Inward Rectifier Current Downregulation Promotes Spontaneous Calcium Release in a Novel Model of Rat Ventricular Electrophysiology

Harley J. Stevenson-Cocks, Michael A. Colman, Ed White, Alan P. Benson

University of Leeds
Leeds, UK

Aberrations in intracellular calcium (Ca^{2+}) handling, in diseases such as heart failure (HF), increase vulnerability to lethal arrhythmias and resultant sudden cardiac death. The underlying mechanisms for these processes are difficult to explore experimentally, but recent data from our laboratory suggests that reduced inward rectifier current (I_{K1}) expression in failing rat myocytes increases pro-arrhythmic spontaneous Ca^{2+} release. However, existing computational models of rat cardiac electrophysiology are unable to capture the complex underlying phenomena, so we have been unable to computationally explore the hypothesis that this results from increased sarcoplasmic reticulum (SR) loading in the presence of a destabilised membrane.

A new computational model was therefore developed by combining a recent rat ventricular electrophysiology model with a novel model of stochastic spatio-temporal Ca^{2+} handling dynamics developed in our laboratory. The newly-developed model was used to dissect and quantify the electrophysiological changes associated with remodelling of I_{K1} and Ca^{2+} homeostasis in HF. A similar reduction in I_{K1} to that observed experimentally resulted in a 57% increase in action potential duration (APD) in simulations, from 58.1 to 91.4 ms. This prolonged APD allowed greater SR loading, leading to raised $[Ca^{2+}]_{SR}$ and more frequent spontaneous release events. These events, in turn, triggered forward-mode sodium-calcium exchange, resulting in triggered action potentials. Resting membrane potential was also depolarised in HF myocytes by 3.3 mV.

The newly-developed model has reproduced experimental results from the laboratory and provided insight into the underlying mechanisms of spontaneous Ca^{2+} release in HF. Thus, it provides a powerful research tool that can be used to explore how HF-induced sub-cellular remodelling may result in arrhythmias at the tissue and organ levels.