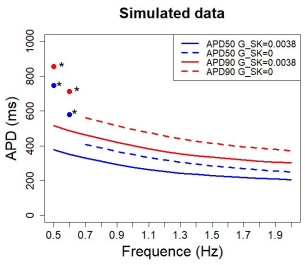
An in Silico Investigation into the Role of SK Channels in Failing Ventricular Myocytes

Marta Gomez, Jesus Carro, Esther Pueyo, Violeta Monasterio

Universidad San Jorge
Zaragoza, España

SK channels are small conductance ($\sim$10 pS) calcium-activated potassium channels. Although they have been suggested not to play a relevant role in healthy ventricles, SK channel upregulation has been reported in failing ventricles, with potential implications for arrhythmogenesis. However, there is conflicting evidence on the pro- or antiarrhythmic role of these channels.

In this work, we aimed at uncovering the contribution of SK channels to ventricular repolarization in failing myocytes. To that end, we extended an in silico electrophysiological model of human ventricular failing myocytes by introducing the equations representing SK channel activity. The value of the conductance G_{SK} was adjusted taking into account experimental observation from human ventricular cells from 7 patients with heart failure (HF). The relative differences in APD_{50} and APD_{90} with and without SK channels block, for 1Hz and 2Hz pacing, were used as reference data. After adjustment, simulations were performed for pacing frequencies between 0.5 and 2 Hz under control conditions. At the lowest frequency, 0.5 Hz, a sensitivity analysis was conducted to determine the influence of ionic conductances on the generation of early after-depolarizations (EADs).



As a result, the optimal value for the conductance was $G_{\text{SK}} = 0,0038\mu S$. Simulations with that value differed from the reference data by a maximum of 1,37% for APD_{50} and by a maximum of 3,49% for APD_{90}. Early afterdepolarizations were observed at pacing frequencies below 0.7 Hz only when SK channels were blocked. Results from the sensitivity analysis indicated that SK current had a major role in EAD formation.

In conclusion, our presented model of human ventricular failing myocytes integrating an SK channel formulation can allow dissecting the contribution of SK channels to ventricular repolarization and may help in understanding their role in arrhythmogenesis.