ABSTRACT CinC 2018

Optimization of the O’Hara-Rudy Model of Human Ventricular Action Potential with Respect to Electrolyte Concentrations and Rate Dependence

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Aims: To improve the most used computational model of human ventricular action potential in order to 1) correct its response to the extracellular calcium concentration ([Ca²⁺]o) changes; 2) to replicate the steady state action potential duration (APD) rate dependency and the S1S2 APD restitution by simulating the same conditions in which the experimental values were obtained (namely at 4 mM extracellular K⁺).

Methods: The O’Hara-Rudy (ORd) human ventricular model was chosen for this study, for its extensively use in the in silico reconstruction. The original I_{CaL} Hodgkin-Huxley description has replaced by a new Markov model, modified the values of some parameters (e.g.: rates on the CDI/VDI loop; the n gate kinetics and some kinetic rates) and the sarcoplasmic reticulum was reduced to a single compartment. In order to preserve the achieved APD-[Ca²⁺]o dependence without altering model behaviour in control condition and gain a well-fitting of the steady state APD rate dependency and the S1S2 APD restitution an optimization procedure was implemented to refine the previous model, modifying some currents which play a role in both protocols.

Results: The present model correctly reproduced the inverse relationship between APD and [Ca²⁺]o ([Ca²⁺]o = [1.2 1.8 2.4]mM, APD₉₀ with our model is [266 237 224] ms vs [243 266 275]ms with ORd).

When setting [K⁺]o = 4mM the experimental data of the S1S2 protocol and of the steady-state rate dependence were very well fitted with all the APD values for almost all the tested frequencies being within the experimental ranges.

Conclusions: The study highlights the importance of reproducing experimental conditions as closely as possible in the simulations to allow an effective comparison between experiments and simulations for validation. More accurate will be the model, more it could be integrated in the used of in silico models for predicting clinical risk of drug-induced arrhythmias.