Optimization of an In Silico Cardiac Cell Model for Proarrhythmia Risk Assessment

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Abstract

The Comprehensive in vitro Proarrhythmia Assay (CiPA) is a regulatory paradigm proposed to replace the ICH S7B and E14 guidelines for assessing drug-induced proarrhythmia. Under CiPA, drug effects on multiple cardiac ion channels will be measured in vitro and integrated into an in silico model of the adult human ventricular cell, based on the O'Hara-Rudy (ORd) model. However, the ORd model does not accurately represent certain ionic currents known to be critical in triggering drug-induced arrhythmias, such as the late sodium current (I_{NaL}). The goal of the present study is to systematically assess and improve the simulation of the main depolarizing and repolarizing ionic currents (the inward rectifying potassium currents, L-type calcium current and I_{NaL}) in the ORd model. We present a new model with scaled conductances calculated by fitting to O'Hara et al. in vitro human cardiomyocyte channel blocking experiments using a genetic algorithm, which improves discrepancies of the original model. The modified model particularly improves the effect of I_{NaL} block on action potential prolongation, an important determinant of proarrhythmia risk in the context of CiPA.

1. Introduction

Torsade-de-pointes (TdP) is a lethal type of arrhythmia that caused removal of several drugs from the market [1] and led to the adoption of the ICH E14 and S7B guidelines to identify TdP risk. Although block of the delayed rectifier potassium current (I_{Kr}) and the 10 ms prolongation of QT criteria set by the guidelines are highly sensitive predictors of TdP risk, they are not specific and may prevent many useful and effective drugs with low TdP risk from entering the market. In an effort to improve the specificity of assessing clinical TdP risk, the Comprehensive in vitro Proarrhythmia Assay (CiPA) collaborative initiative was established [2]. The aim of this regulatory paradigm is to combine measurements of multiple cardiac ionic currents with in silico modeling to predict TdP risk, coupled with stem cell and clinical ECG studies to confirm those predictions or identify mechanisms missing from the patch clamp data sets. The O'Hara et al. model (ORd) was chosen as the consensus base model [3].

As part of CiPA, an initial set of 12 drugs determined by cardiologists to have low, intermediate or high risk of TdP were selected to form a training set. Many of the CiPA drugs are multi-channel blockers, particularly the low risk drugs [4]–[6]. However, simulations of drug effects using the current version of the ORd model and latest patch clamp data show discrepancies with results on human cardiomyocytes, suggesting some currents (eg. the late sodium current, I_{NaL}) are not correctly represented.

The aim of this study is to improve the ORd model so that it accurately simulates the changes in action potential duration (APD) produced by drugs that block multiple ion channels.

2. Methods

2.1. Simulation protocol

All simulations were run using the ORd endocardial cell model for 1000 beats at varying cycle lengths (CLs) 500, 1000, 2000 and 4000 ms. Drug block was simulated using the Hill function and data from Crumb et al. [7] for varying drug concentrations: free plasma clinical drug exposures (Cmax) up to 20X Cmax. APD was calculated as the time taken for the transmembrane potential (V_m) of the cell to reach 90% (APD90), 70% (APD70), 50% (APD50) and 30% (APD30) of its resting V_m. ΔAPD was calculated as the percentage difference in APD prolongation between control and drug. Simulations were run in R and C using the deSolve package.

2.2. Modified ORd model

The original ORd model was modified by scaling conductances as follows: I_{Kr} by 1.119, the slow rectifier potassium current (I_{Ks}) by 1.648, the inwardly rectifying potassium current (I_{K1}) by 1.414, the L-type calcium current (I_{CaL}) by 1.018 and I_{NaL} by 2.274. These values were calculated by fitting to experimental data from

O'Hara et al. using a Genetic Algorithm-based Parameterization for Systems Modeling [8]. Briefly, an initial set of parameters are defined within a certain range and their goodness of fit is assessed using an objective function defined as the weighted sum of the squared errors between model values and experimental measurements. The set of parameters then undergoes various changes (i.e. mutation and recombination) to create a new generation of parameters and this process is continued until a global optimum is reached.

The experimental data used in the algorithm are taken from the ORd model paper [3] and shows APD rate dependence for control and 5 drug blocking conditions: 1 μM E-4031 (70% I_{Kr} block), 1 μM HMR-1556 (90% I_{Ks} block), 1 μM nisoldipine (90% I_{CaL} block), 100 μM BaCl2 (90% I_{K1} block), 10 μM mexiletine (54% I_{NaL}, 9% I_{Kr}, and 20% I_{CaL} block). The simulated block was kept the same as in the ORd paper, apart from mexiletine, which was simulated using IC50 and hill coefficient data from Crumb et al. [8]. The algorithm was run using in-house developed R scripts and parallel computing Snow and Rmpi packages on the FDA High Performance Computer (HPC) with 160 cores.

3. Results

3.1. Fitting to experimental data

The modified ORd model was built by refitting to APD rate dependence experimental data from O'Hara et al., as shown in Figure 1 and Table 1. The goodness of fit of each set of parameters generated by the genetic algorithm was tested by calculating the sum of squares error as in Table 1. The best parameters were passed onto the next generation and the rest underwent mutation, recombination, migration and repopulation to create the new set of parameters. Here we present the best parameters that showed the smallest error.

Under control conditions both the original and modified models display a similar behavior, although APD90 is shorter in the modified ORd. However, the overall error under control conditions is smaller for the modified ORd (15.01) than the original ORd (17.20) models (see Table 1). Furthermore, the modified ORd model shows a better fit to the experimental data for the I_{NaL}, I_{CaL} and I_{Kr} blockers (23.98 vs. 92.92; 0.75 vs. 5.29; 145.03 vs. 15.96) while the two models show similar results for the I_{Ks} blocker (HMR-1556). Finally, the modified ORd shows good agreement with experimental data for faster CLs ≤ 1000 ms for the I_{K1} blocker ($BaCl_2$). Therefore, overall the modified ORd displays a closer match to experimental data (average error of 19.85 vs. 57.77). The main improvements are observed for the I_{NaL} and I_{Kr} blockers, mexiletine and E-4031.

3.2. AP and current traces of the models

As described in the methods all of the current conductances are increased in the modified ORd model, however, the AP shape of both models is very similar, as shown in Figure 2. The smallest change in current amplitude observed is I_{CaL}, which only has a 1.8% change in conductance. However, clear differences are observed for all other currents (I_{Kr}, I_{NaL}, I_{Ks} and I_{K1}) with the biggest changes occurring for I_{NaL} (conductance is increased by 227%) and I_{Ks} (conductance is increased by 165%). Therefore, I_{NaL} plays a bigger role in the modified ORd model given there is a greater increase in I_{NaL} compared to I_{Kr}.

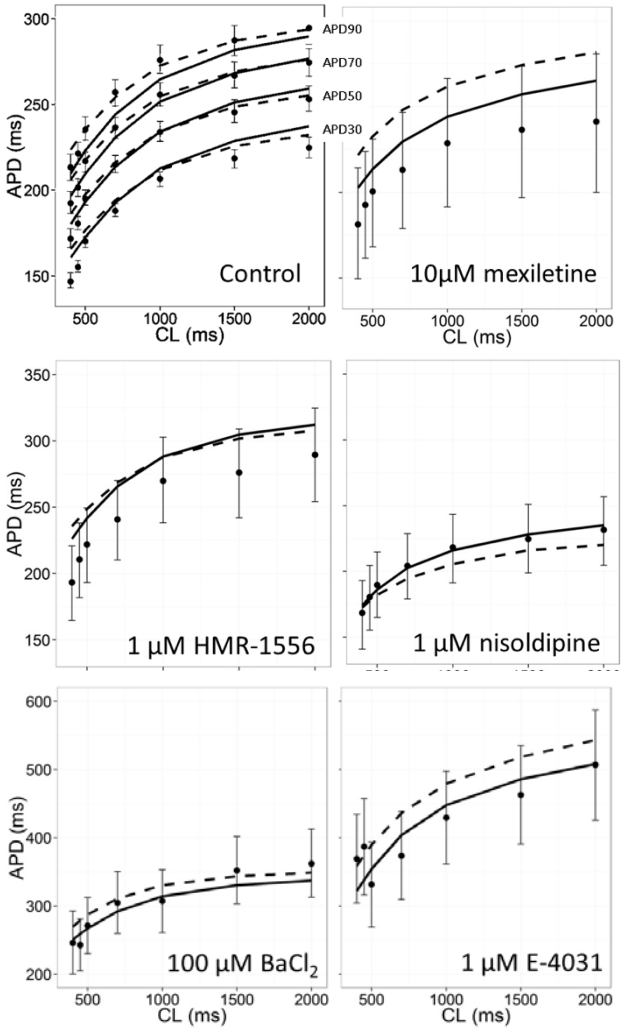

Figure 1. Control, 10 μM mexiletine, 1 μM HMR-1556, 1 μM nisoldipine, 100 μM $BACl_2$ and 1 μM E-4031 steady state APD rate dependence for varying cycle lengths (CLs) for the original O'Hara et al. (ORd; dashed lines), the modified ORd model (solid line) and experimental data mean and standard deviation from O'Hara et al. [3] (error bars). Control shows action potential duration

(APD) at 90% (APD90), 70% (APD70), 50% (APD50) and 30% (APD30) repolarization. All other panels show APD90.

Table 1. Sum of squares error between APD rate dependence experimental data mean and simulation results (see Figure 1) for the original ORd and the modified ORd.

Sum of squares error	Original ORd	Modified ORd
Control	17.2	15.01
10 μM mexiletine	92.92	23.98
1 μM HMR-1556	56.35	43.54
1 μM E-4031	145.03	15.96
100 μM $BaCl_2$	29.83	15.96
1 μM nisoldipine	5.29	0.75
Average ± SD	**57.77 ± 52.98**	**19.85 ± 16.67**

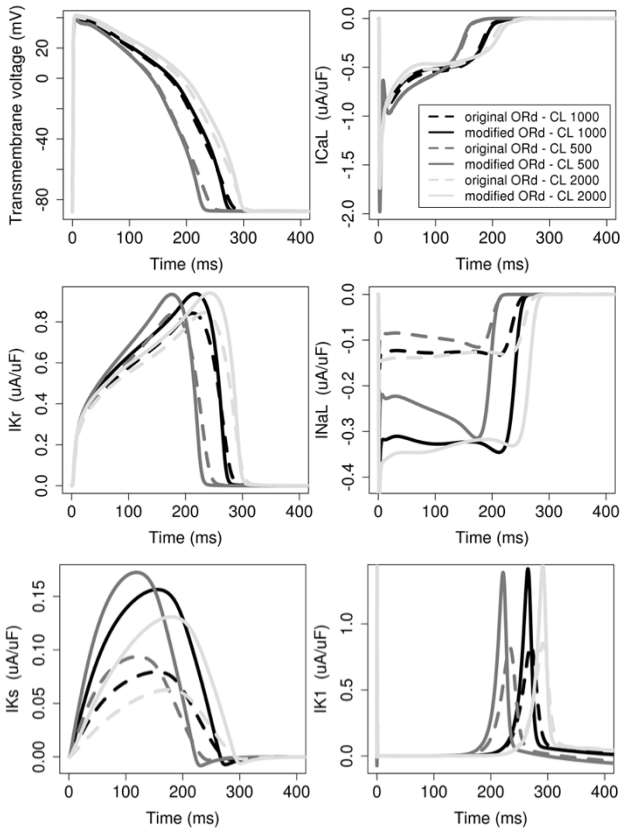

Figure 2. Action potential (AP), L-type calcium current (I_{CaL}), delayed rectifier potassium current (I_{Kr}), late sodium current (I_{NaL}), slow rectifier potassium current (I_{Ks}) and inwardly rectifying potassium current (I_{K1}) traces under control conditions for the original ORd (dashed line) and the modified ORd (solid line) for CLs of 500 (dark gray), 1000 (black) and 2000 (light gray) ms.

3.3. Drug-induced APD prolongation

Block of I_{NaL} is underestimated and block of I_{Kr} is overestimated in the original ORd model, as shown in Figure 3. The modified ORd shows a smaller APD prolongation for 75% I_{Kr} block compared to the original ORd (192.5 ms vs 238.52 ms) and a greater decrease in APD for 75% I_{NaL} block (42.51 ms vs. 16.5 ms). As shown in Figure 1, this is closer to the experimental data with E-4031, a potent I_{Kr} blocker, and mexiletine, a potent I_{NaL} blocker. Proper characterization of I_{NaL} block in the model is important as it plays an important role in counteracting pro-arrhythmic APD prolongation of I_{Kr} block.

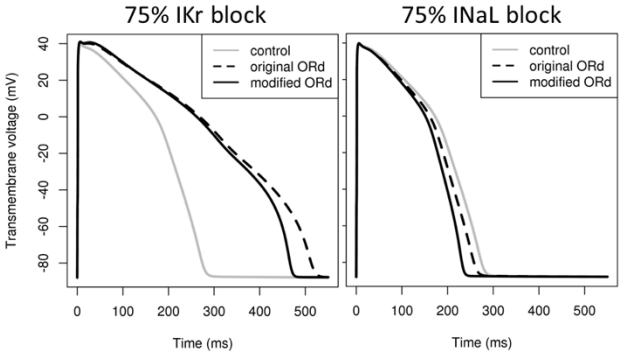

Figure 3. AP traces for 75% I_{Kr} (left panel) and I_{NaL} block (right panel); original ORd (dashed black line); modified ORd (solid black line); control (gray).

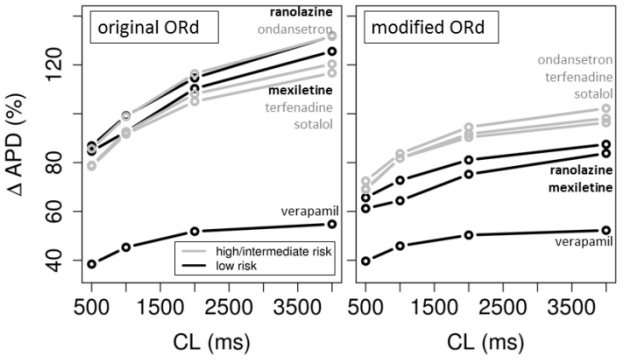

Figure 4. Original ORd (left panel) and modified ORd (right panel) ΔAPD (%) with a CL of 500, 1000, 2000 and 4000 ms and 20X Cmax for a subset of the CiPA drugs (high/intermediate risk in gray and low risk in black).

The increased effect of I_{NaL} is demonstrated in Figure 4, which shows APDs for varying CLs in both models for a subset of the CiPA drugs. As expected for all models the APD prolongation increases as the CL increases. However, in the original ORd model ranolazine and mexiletine (I_{NaL} blockers) show an increase in APD similar to other high and intermediate risk drugs. This is improved in the modified ORd model, where the APD

prolongation of the I_{NaL} blockers is closer to other safe drugs such as verapamil (I_{CaL} blocker) and is clearly separated from higher risk drugs. Therefore, the separation between the safe risk category and the intermediate and high risk categories is improved in the modified ORd model.

5. Discussion

This study presents a modified ORd model with a new set of scaling conductances for the I_{Kr}, I_{NaL}, I_{CaL}, I_{Ks} and I_{K1} currents that better fit APD rate dependence experimental data, improve the prediction of I_{NaL} block on APD and the separation of the low TdP risk CiPA drugs from the intermediate and high risk CiPA drugs.

This study has certain limitations that should be taken into account. Firstly, IC50 current blocking data for high Cmax were extrapolated in some cases as the concentrations simulated were higher than the experimental concentrations tested by Crumb et al., as was the case for the I_{Kr} blocking effect of mexiletine [7]. Secondly, APD, like QT, is not a predictive marker of drug-induced TdP risk [2]; therefore this metric is presented to show the change in APD prolongation induced by I_{CaL} and I_{NaL} block rather than attempting to show clear separation between the TdP risk categories. The authors of this study are investigating other more specific and sensitive metrics of TdP risk. Thirdly, dynamics of the I_{Kr} current play an important role in the risk of TdP, particularly for high and intermediate risk drugs [9], [10], and therefore, an updated ORd model is currently being developed based on our previously published model [11]. Finally as shown in Figure 1, despite the change in I_{Ks}, the original and modified ORd models show similar results due to changes in I_{Ks} having little effect on APD, as shown previously [12], however under certain conditions, such as beta-stimulation, effects may be more pronounced.

In conclusion, this study presents important results for the development of a modified ORd human ventricular action potential model that can more accurately predict drug-induced TdP, particularly in the presence of I_{NaL} block.

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