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Convergence of models of human ventricular myocyte electrophysiology after global optimization to recapitulate clinical long QT phenotypes

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ABSTRACT

In-silico models of human cardiac electrophysiology are now being considered for prediction of cardiotoxicity as part of the preclinical assessment phase of all new drugs. We ask the question whether any of the available models are actually fit for this purpose. We tested three models of the human ventricular action potential, the O'hara-Rudy (ORD11), the Grandi-Bers (GB10) and the Ten Tusscher (TT06) models. We extracted clinical QT data for LQTS1 and LQTS2 patients with nonsense mutations that would be predicted to cause 50% loss of function in I_{Ks} and I_{Kr} respectively. We also obtained clinical QT data for LQTS3 patients. We then used a global optimization approach to improve the existing in silico models so that they reproduced all three clinical data sets more closely. We also examined the effects of adrenergic stimulation in the different LQTS subsets. All models, in their original form, produce markedly different and unrealistic predictions of QT prolongation for LQTS1, 2 and 3. After global optimization of the maximum conductances for membrane channels, all models have similar current densities during the action potential, despite differences in kinetic properties of the channels in the different models, and more closely reproduce the prolongation of repolarization seen in all LQTS subtypes. *In-silico* models of cardiac electrophysiology have the potential to be tremendously useful in complementing traditional preclinical drug testing studies. However, our results demonstrate they should be carefully validated and optimized to clinical data before they can be used for this purpose.

1. Introduction

Over the last 50 years, efforts to model the cardiac action potential and the electrocardiogram have evolved to the stage where they stand at the threshold of clinical application [1]. For example, the Food and Drug Administration (FDA) sponsored Comprehensive In Vitro Proarrhythmia Assay (CiPA) initiative, aimed at better pro-arrhythmic risk stratification for new drug entities, has *in-silico* modeling at its core [2]. However, while there is no doubt that computational models are invaluable tools for quantitative hypothesis testing [3], one must be cautious about using models to extrapolate to systems beyond the constraints that were used to develop the model in the first place.

Many models of the ventricular action potential have been published over the last decade (e.g. [4–6]). A more comprehensive list of models (for human, as well as other species) can be accessed from the CellML repository [7]. When considering these models, it is striking that there are considerable differences between them both in terms of the gating kinetics as well as the maximal conductance of the membrane currents that contribute to repolarization. One possibility is that these different models each represent individual 'good enough' solutions that occur amongst the large population of possible solutions that can reproduce the normal action potential at baseline [8–11]. An alternative possibility is that they are optimized solutions based on partial datasets and so are sub optimal for predicting outcomes in different circumstances.

Abbreviations: LQTS, long-QT syndrome; VM, ventricular myocyte; APD, Action potential duration; I_{Kr}, rapidly activating delayed rectifier current; I_{Ks}, slowly activating delayed rectifier current; I_{NaL}, late (persistent) sodium current; I_{CaL}, L-type calcium current; NCX, Sodium-calcium exchanger; NaK, Sodium-potassium pump.

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Congenital LQTS is a genetically heterogeneous condition, with at least 14 different genetic subtypes [12]. The major subtypes are LQTS1, which is caused by mutations in *KCNQ1* and results in reduced I_{Ks} current; LQTS2, which is caused by mutations in *KCNH2* and results in reduced I_{Kr} current; and LQTS3, which is caused by mutations in *SCN5a* resulting in an increased level of the late sodium current (I_{NaL}) [13]. Given that these genetically determined conditions all result in similar phenotypes, despite very different molecular bases, we reasoned that the extent of prolongation of repolarization caused by these different genetic subtypes of LQTS should provide a useful dataset with which to constrain *in silico* models of the human ventricular action potential.

In this study, we show that three contemporary models of the human ventricular action potential which we refer to as TT06 [4]; GB10 [5] and ORD11 [6] do not reproduce the clinically observed QT prolongation seen in the congenital Long QT syndromes. We then test the hypothesis that a global optimization of the expression levels of cardiac ion channels within *in-silico* models can be performed using constraints from QT data for different subtypes of LQTS. Furthermore, since subtypes of the long QT syndrome are differentially modulated by sympathetic tone [14], we use published data describing the effect of epinephrine infusion on changes in QT interval in different subtypes of LQTS to determine adrenergic control of the repolarization reserve. Following global optimization, all models tested reproduce clinical QT data more faithfully.

2. Methods

2.1. Clinical datasets

Data were obtained from the International LQTS registry database held at the University of Rochester Medical Centre, NY and the Centre for Cardiovascular Genetics, Umeå University, Umeå, Sweden. Four cohorts were collected. Patients with heterozygote nonsense mutations in *KCNQ1* (LQTS1 cohort), heterozygote nonsense mutations in *KCNH2* (LQTS2 cohort), heterozygote mutations in *SCN5a* (LQTS3) and the genotype-negative siblings of affected individuals in the three genetic subtypes (control cohort). We chose to focus on nonsense mutations in LQTS1 and LQTS2 as there is a large number of these mutations and even when nonsense mutations are in different locations within the transcript they should undergo nonsense-mediated decay [15] and so result in 50% reduction in channel function. We could not do this for LQTS3 as SCN5a mutations in LQTS result in a gain of function and so we have included all heterozygote mutations for this cohort.

Baseline QTc measurements were typically obtained from lead II on standard resting 12-lead electrocardiograms. Mean QT interval of at least three consecutive beats, corrected for heart rate using the RR interval preceding the beats were corrected using Bazett's formula: $QTc = QT / \sqrt{RR}$. To minimize the confounding influence of patient specific variation in the heart rate dependence of QT intervals [16], we restricted our analysis to patients who had a resting heart rate of <70 beats per minute.

Data for the influence of epinephrine infusion on changes in QT interval in different genetic subtypes were derived from the data presented by Ackerman and colleagues [14] (see Fig. 1).

2.2. Model simulations

Simulations were carried out in Matlab 2016a. The ORD11 model was downloaded from the Rudy Lab website (http://rudylab.wustl.edu/). The TT06 model was downloaded from the CellML repository (https://www.cellml.org/) and converted into Matlab code using Cellular Open Resource [17]. E. Grandi kindly provided the GB10 model code (https://somapp.ucdavis.edu.edu/Pharamcology/bers/). All models were run in the endocardial configuration. Following a change in any parameter the model outputs will take a variable number of beats to reach a new steady-state, depending on the model as well as which parameter was changed. We determined that it took up to 450 beats for the ORD11 model to come to steady-state for any change in parameter, ~200 beats for the TT06 model and ~150 beats for the GB10 model. In our optimization routines we therefore ran each model for this corresponding number of beats before calculating the APD_{90} values for that parameter set.

Long QT syndrome phenotypes were modeled by reducing I_{Ks} by 50% (LQTS1), reducing I_{Kr} by 50% (LQTS2) or increasing the late sodium current I_{NaL} (LQTS3). For the TT06 and GB10 models, which do not contain a description of I_{NaL}, we introduced the I_{NaL} description from the ORD11 model. In ORD11, CaMK modulates a proportion of the fast I_{Na} as well as I_{NaL} [6]. The proportion of channels affected by this does not exceed 15%, and the modulation is of minor significance for I_{NaL} (data not shown). Because of the differences in implementation of Ca^{2+} handling between the models, when implementing I_{NaL} in the TT06 and GB10 models we did not include the modulation by CaMK.

2.3. Parameter optimization

For the parameter optimization problem the objective function we were solving was a set of simulated APD_{90} outputs. As it was not possible to determine the first or second derivatives of the objective function, we were not able to use gradient search methods but instead used a pattern search algorithm. This was implemented using the "patternsearch" function in the Matlab Global Optimization Toolbox, Mathworks, Natick, MA, USA. For each of the channels, transporters and pumps chosen for our optimization process, we included simple scaling factors for the maximum conductance in the models. Specifically, we included scaling factors for I_{Kr}, I_{Ks}, I_{CaL}, I_{NaL}, I_{NaCa} and I_{NaK}. We also applied scaling factors to the degree of upregulation of I_{CaL} and I_{Ks} that occurs under increased adrenergic tone, as well as the degree of upregulation of I_{NaL} that occurs in LQTS3 (see Fig. 4). We did not modify the voltage dependence of gating in any of the descriptions. For each iteration of the optimization routine, the values for these scalars were varied and the models were paced until they reached steady-state (see above). APD_{90} was determined by an automated algorithm and expressed as a % prolongation with respect to the baseline APD_{90} at 60 bpm for each model. APD_{90} prolongation factors were compared to the target values compiled from the clinical data (see Fig. 1 below). The optimization minimized the sum of squares of the errors for 8 different outputs (correct baseline APD_{90}, correct adrenergic shortening in CTRL, correct baseline prolongation in LQTS1–3, and correct prolongation in LQTS1–3 under adrenergic conditions) to achieve amounts of APD_{90} prolongation that closely resembled QT prolongation in our clinical datasets (see also Fig. 4 below).

The optimization procedure employed does not allow for generation of confidence intervals for each modified scalar. We therefore investigated how sensitive the final solution, i.e. the minimized sum of squares of the errors for all 8 outputs (correct baseline APD_{90}, correct adrenergic shortening in CTRL, correct baseline prolongation in LQTS1–3, and correct prolongation in LQTS1–3 under adrenergic condition) was to small perturbations in each parameter. From this analysis, we calculated sensitivity coefficients (ρ) for each parameter estimate as previously described [18,19] (see Table 1 below).

2.4. Population distribution

To model population distributions of action potential durations in the different cohorts each of the ionic conductances was scaled by a different random number generated from a log–normal distribution with a mean value of 1 and variance set at 0.05, as previously described [18,19].

3. Results

3.1. QT prolongation in clinical cohorts of LQTS patients

Frequency distributions of QTc values for control, LQTS1, LQTS2 and LQTS3 patients are shown in Fig. 1. The mean QTc values were 412 ± 27 ms (mean ± SD, $n = 196$) for controls, 463 ± 31 ms (mean ± SD,