Recent Human Ventricular Cell Action Potential Models Under Varied Ischaemic Conditions

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Abstract

Investigating arrhythmic mechanisms during ischaemia is essential to improve clinical therapy. However, experimental data in human is scarce. Computational models are an essential tool for bridging this gap. Recent human ventricular cell action potential (AP) models have been built with data from healthy cells, thus their applicability to studies of ischaemia is mostly unknown. We have carried out a simulation study in single cell and tissue under normal and varied ischaemic conditions using 4 recent human models: ten Tusscher et al. 2006 (TP06), Grandi et al. 2010 (GPB), Carro et al. 2011 (CRLP), and O'hara et al. 2011 (ORd). We varied two parameters that play an important role in arrhythmogenesis during ischaemia: extracellular potassium concentration ($[K^+]_o$) and peak conductance of the ATP-sensitive inward-rectifying potassium current ($I_{K(ATP)}$). To assess the applicability of these models to simulate ischaemia, we calculated AP duration (APD) and post-repolarisation refractoriness (PRR), biomarkers of arrhythmic risk. Results show that all models displayed the expected APD shortening due to $I_{K(ATP)}$ activation and hyperkalaemia. Furthermore, all models, apart from the ORd, reproduced an increase in PRR. The GPB did not show propagation of excitation for $[K^+]_o$*=9mM. This study suggests that the CRLP and TP06 models are the most suitable for performing human-specific simulations of arrhythmogenesis during myocardial ischaemia.*

1. Introduction

One of the major causes of cardiac arrest is acute myocardial ischaemia. It is a dynamic and complex process that increases electrophysiological heterogeneities across the heart and the likelihood of developing arrhythmias. The main physiological changes that occur during the early phase of ischaemia (first 10-15min), the time interval associated with greatest pro-arrhythmic risk, are hyperkalaemia, resulting in an increase in $[K^+]_o$, hypoxia, resulting in an opening of $I_{K(ATP)}$ channels, and acidosis, which decreases the conductances of the sodium (I_{Na}) and L-type calcium (I_{CaL}) currents [1]. This induces changes in biomarkers related to arrhythmias, such as a reduction in APD and a prolongation of PRR (the time between cell repolarisation and re-excitability).

Most research on ischaemia has been carried out in animals, and data from human is scarce. Computational models are an essential tool to increase our understanding of ischaemia-induced arrhythmic mechanisms in human [2]. However, most of the recent human models are created and validated with data from healthy cells. Their applicability for simulations of ischaemia is unknown.

The aim of this study was to provide an informed investigation of the response of 4 recent human models (TP06, GPB, CRLP, and ORd) to varied ischaemic conditions by comparing APD and PRR in single cell and tissue simulations to experimental data, in order to assess their utility for studying mechanisms of arrhythmogenesis in ischaemia.

2. Methods

2.1. Action potential models

In this study we investigate 4 recent human ventricular action potential models. The TP06 model has been widely used, but is limited in its representation of calcium dynamics [3]. The GPB [4] and the CRLP models [5] are similar. The latter model modified and reformulated various currents from the GPB model, such as I_{CaL} and I_{K1}, to better fit restitution properties to experimental ranges. The ORd model [6] reformulates most major ionic currents based on human data from over 100 undiseased human hearts. Major components modelling the dynamics of the Ca^{2+}/calmodulin-dependent protein kinase II were added to important ionic currents, such as I_{Na} and I_{CaL}.

2.2. Ischaemic electrophysiological changes

To simulate ischaemia, peak I_{Na} and I_{CaL} conductances were decreased by 25%, and the two main parame-

ters affecting APD and PRR were varied as follows: $[K^+]_o$ increased from 4 to 9mM, in steps of 1mM, and peak $I_{K(ATP)}$ conductance was increased from 0 to 20%, in steps of 2% in single cell and 4% in tissue.

The $I_{K(ATP)}$ current, shown in Equation 1, was added to the cell models using COR [7]. The amplitude of the current depends on the ratio of the existing extracellular potassium concentration, $[K^+]_o$, and the normal extracellular potassium concentration, $[K^+]_{o,n}$. It also depends on the voltage of the cell, V_m, and the reversal potential of potassium, E_K. We used the value estimated by Michailova *et al.* [8] for the channel conductance ($G_{K(ATP)}$=0.05mS.μF^{-1}) and used $f_{K(ATP)}$ as a scaling factor to vary peak $I_{K(ATP)}$ conductance:

$$I_{K(ATP)} = G_{K(ATP)} f_{K(ATP)} \left(\frac{[K^+]_o}{[K^+]_{o,n}} \right)^{0.24} (V_m - E_K). \quad (1)$$

2.3. Single cell and tissue simulations

Single cell simulations were run in MATLAB. Equations were solved using *ode15s* with a maximum time step of 1.0ms, and a relative and absolute tolerance of 10^{-7} and 10^{-9} to ensure numerical convergence. Stimulus duration was set to 2ms and the amplitude to 2 times the activation threshold. Effective refractory period (ERP), used to calculate PRR, was determined by running the cell to steady state with a stimulus period of 1000ms (S1), and then applying a stimulus at progressively shorter periods (S2), in intervals of 10ms. ERP was calculated as the minimum S2 period (greater than the APD) that triggered an action potential (defined as a plateau voltage above -20 mV).

Tissue simulations were run using Chaste [9] on a 5cm long 1D strand of coupled cells. The space discretisation was 0.01cm and the ode and pde time steps were set to 0.005ms and 0.01ms for the CRLP and GPB models and 0.001ms and 0.01ms for the TP06 model, which ensured convergence of results. ERP was assessed in a similar manner as in the cell simulations. The tissue was stimulated with $-10^6\mu$A.cm^{-3} for 0.5ms at position x=0cm for 5 beats with an S1 period of 1000ms, followed by decreasing S2 stimuli, with ERP calculated as the minimum S2 that triggered an AP in the cell at position x=3cm. In both single cell and tissue, the APD was calculated at 90% repolarisation and the PRR as the difference between ERP and APD.

3. Results

3.1. Single cell results

We investigated the behaviour of 4 models under varying ischaemic conditions in single cell simulations by comparing APD and PRR values, biomarkers related to arrhythmic risk. Results presented in Figure 1 show that in all models, as peak $I_{K(ATP)}$ (represented as $f_{K(ATP)}$) and $[K^+]_o$ increased, the APD decreased. Figure 2 shows that the PRR of all the models, apart from the ORd model, increased as peak $I_{K(ATP)}$ and $[K^+]_o$ increased (with a relatively greater increase due to a change in $[K^+]_o$).

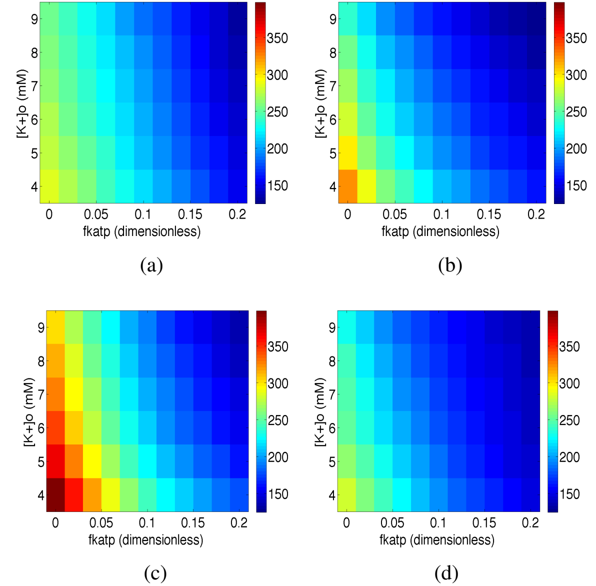

Figure 1. Single cell results: comparison of APD (ms) of different models ((a) TP06, (b) GPB, (c) CRLP, and (d) ORd) to variations in $[K^+]_o$ (4-9mM) and in peak $I_{K(ATP)}$ conductance scaling factor $f_{K(ATP)}$ (0-20%).

3.2. Tissue results

We next conducted a study in tissue to investigate ischaemia-induced effects on electrical propagation with the different models. The ORd model was not tested as it did not reproduce the expected changes in PRR with ischaemia in the single cell simulations (see Figure 2). Results in tissue show that all models exhibited a similar behaviour, a reduction in APD and increase in PRR (Figure 3) as peak $I_{K(ATP)}$ and $[K^+]_o$ increased. The GPB model, however, demonstrated propagation failure for $[K^+]_o$=9mM. Further analysis, shown in Figure 4, suggested that this may be due to the I_{Na} h-gate having a lower steady state value than with the TP06 and CRLP models. Figure 5 shows the transmembrane potential and the PRR of the TP06 and CRLP models for two sets of parameter values: $f_{K(ATP)}$=8% and $[K^+]_o$=5 and 9mM. It is clear that even though both propagate in tissue, with $[K^+]_o$=9mM the TP06 model displayed a full AP, while the CRLP model did not.

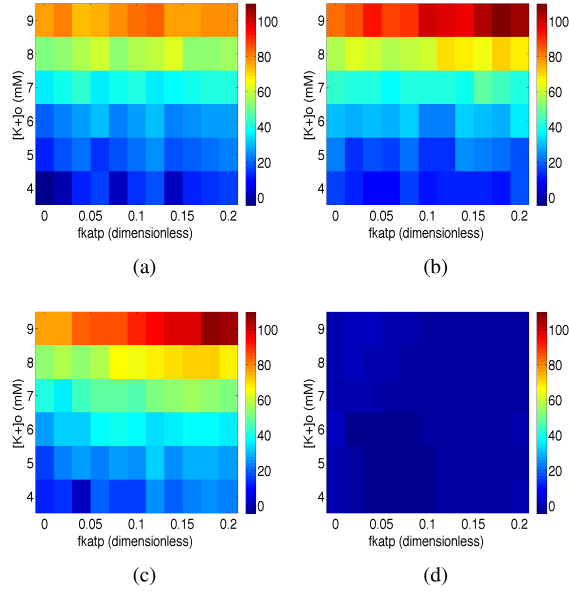

Figure 2. Single cell results: comparison of PRR (ms) of different models ((a) TP06, (b) GPB, (c) CRLP, and (d) ORd) to variations in $[K^+]_o$ (4-9mM) and in peak $I_{K(ATP)}$ conductance scaling factor $f_{K(ATP)}$ (0-20%).

3.3. Comparison to experimental data

Sutton *et al.* have carried out epicardial electrogram recordings in human hearts during 3min of simulated ischaemia [10]. Their APD and PRR results are summarised in Table 1, along with our results. When comparing the two, it is important to take into account the difference in time of ischaemia. Our simulations simulated ischaemia up to 10-15min post occlusion. Taking this into account, Table 1 shows that the range of values observed in our simulations in single cell and tissue are comparable to the ones observed experimentally.

Table 1. Comparing APD and PRR simulation results (single cell/tissue results) to experimental data in human carried out by Sutton *et al.* [10]. The range of values goes from control to ischaemic conditions.

	APD	PRR
Sutton *et al.*	260-180ms	0-120ms
TP06	270-150ms/270 -150ms	10-80ms/0-350ms
GPB	290-150ms/270-50ms	10-100ms/0-250ms
CRLP	350-150ms/270-150ms	10-100ms/0-260ms
ORd	270-150ms	0-0ms

4. Discussion and conclusions

This study investigated the behaviour of 4 recent human models during ischaemia. This was done by comparing

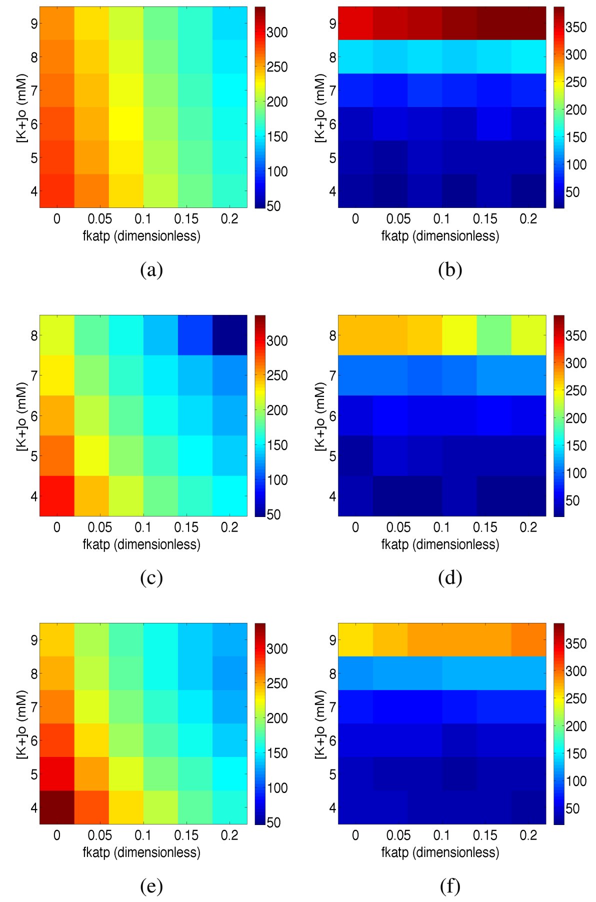

Figure 3. Tissue results: comparison of APD (ms) ((a), (c), and (e)) and PRR ((b), (d), and (f)) of different models ((a) and (b) TP06, (c) and (d) GPB, and (e) and (f) CRLP) to variations in $[K^+]_o$ (4-9 mM) and in peak $I_{K(ATP)}$ conductance scaling factor $f_{K(ATP)}$ (0-20%).

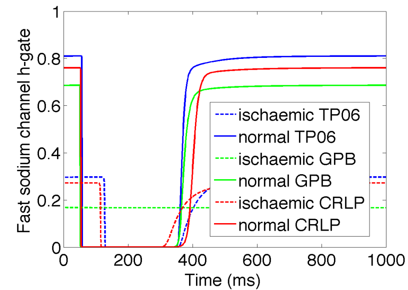

Figure 4. I_{Na} h-gate through time for the 3 different models: TP06 (blue), GPB (green), and CRLP (red). The solid lines are taken under normal conditions ($[K^+]_o$=5 mM, $f_{K(ATP)}$=0%, I_{Na} and I_{CaL} conductances unchanged), and the dashed lines represent the cell models under ischaemic conditions ($[K^+]_o$=9 mM, $f_{K(ATP)}$=4%, peak I_{Na} and I_{CaL} conductances decreased by 25%).

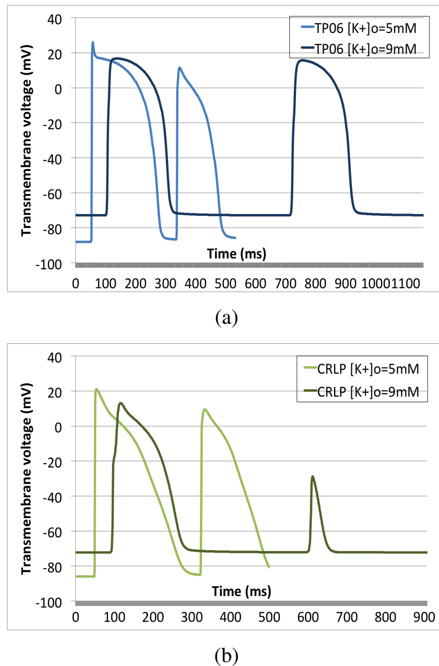

Figure 5. Tissue results: Transmembrane voltage through time showing the smallest second stimulus that triggers propagation with the (a) TP06 and (b) CRLP models for $f_{K(ATP}$=8% and $[K^+]_o$=5 and 9mM.

biomarkers related to arrhythmic risk (APD and PRR) under varying degrees of ischaemia in single cell and tissue.

We compared our results to data from human carried out by Sutton *et al.* to assess whether the models displayed expected ischaemic changes [10]. Firstly, we observed that all models displayed the expected decrease in APD under ischaemia in single cell and tissue, as well as an increase in PRR, apart from the ORd model. The lack of refractory period with the latter model may be due to its I_{Na} specification. Secondly, the GPB did not show propagation for $[K^+]_o$=9 mM, although it did reproduce the expected changes for other ischaemic values. This may be due to the kinetics of the h-gate of I_{Na}, as shown in Figure 4. Finally, we observed that in tissue the TP06 and CRLP models displayed differences in AP characteristics; for $[K^+]_o$=9mM, the TP06 model displayed a full AP, while the CRLP model did not, as shown in Figure 5. Both behaviours may play important roles in arrhythmia-induction.

Results from this study are useful for the selection of a cell model to perform human-specific simulations of myocardial ischaemia. They demonstrate the importance of considering multiple biomarkers at both the single cell and tissue levels simulations to assess the applicability of cell models. Finally, this study provides important insights into the behaviour of the tested models under varied ischaemic conditions, expanding our knowledge of their greater utility. Overall, this work represents an important stepping stone in our pursuit to uncover arrhythmic mechanisms during ischaemia in human.

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