

# A Comparison of Two Models of Human Ventricular Tissue: Simulated Ischaemia and Re-entry

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## Abstract

*Several models of the human ventricular action potential have been developed. The aim of this study was to compare the dynamical behaviour and impact of simulated ischaemia in two cell models: the O'Hara-Rudy dynamic (ORd) model, and the Ten Tusscher-Panfilov 2006 (TP06) model. The endocardial variant of each cellular model was embedded in a 2D monodomain tissue model, and solved with an explicit finite differences approach with a fixed space step of 0.2 mm and time step of 0.005 ms. Action potential duration (APD) and conduction velocity (CV) restitution were measured using an SIS2 protocol with  $S1=1000$ ms. Despite different formulations for both transmembrane currents and calcium handling in these models, the dynamical behaviour and their response to simulated ischaemia in these models was similar.*

## 1. Introduction

Ventricular tachyarrhythmias are one of the main causes of sudden cardiac death. An important consequence of reduced cardiac output during tachyarrhythmias is global cardiac ischaemia, caused by a lack of oxygen-rich blood to the heart, which leads to tissue hypoxia (reduced oxygen) or anoxia as well as an elevation of extracellular  $K^+$ .

In this study, a computational model of human cardiac cells and tissue was used to assess how the metabolic changes associated with ischaemia influence arrhythmia mechanisms. Computational models of cardiac electrophysiology are becoming powerful research tools, which are increasingly used to explain experimental observations. This effort is important in determining the role of ischemic abnormalities in cardiac electrophysiology behaviour, because many of the important parameters are difficult or impossible to observe experimentally [1].

Models of human cell and tissue electrophysiology have been difficult to develop because until recently experimental data from normal human cells was limited

[2]. However, several models of human ventricular cells are now available, and so an important aim of this study was to compare two models of human ventricular myocytes in order to examine the way that cardiac ischaemia influences action potential duration (APD) and conduction velocity (CV) restitution, and the period and stability of re-entry.

## 2. Methods

We used the O'Hara-Rudy dynamic (ORd) model [3] and the Ten Tusscher Panfilov 2006 (TP06) model [4] to represent human cellular electrophysiology. The ORd model is a detailed model for human cells that has been developed recently from human experimental data, whereas the older TP06 model is based on a mixture of human and animal data. The parameters for endocardial cells were used, with modifications to simulate ischaemia that are described in detail below.

Extracellular potassium concentration was elevated from its default value of 5.4 mM to values between 6.0 and 8.0 mM. In both models we added an ATP activated  $K^+$  current  $I_{K,ATP}$  as described by Shaw and Rudy [5]. Anoxia was simulated by reducing intracellular ATP concentration from its normal value of 6.8 mM to 6.0, 5.0, and 4.0 mM with subsequent activation of the ATP sensitive potassium current. The half maximal saturation of  $I_{K,ATP}$ ,  $k_{ATP}$ , was varied between 0.042 mM for a normal value  $[ATP]_i$  of 6.8 mM, 0.117 mM for reduced  $[ATP]_i$  of 6.0 mM, 0.212 mM for reduced  $[ATP]_i$  of 5.0 mM, and 0.306 mM for reduced  $[ATP]_i$  of 4.0 mM. To obtain stable re-entry in the ORd model, the  $Na^+$  current formulation was replaced by the  $Na^+$  current formulation from the TP06 model.

Each model was embedded in a 2D monodomain tissue model [6] with isotropic diffusion, a diffusion coefficient of  $1.171 \text{ cm}^2 \text{ s}^{-1}$  (TP06 model),  $0.2975 \text{ cm}^2 \text{ s}^{-1}$  (ORd model), and a specific capacitance of  $1 \text{ } \mu\text{F cm}^{-2}$  to characterize restitution properties and examine re-entry period. These models were solved with an explicit finite difference approach with a fixed space step of 0.2 mm and time step of 0.005 ms. No-flux boundary conditions were imposed at each edge by setting the gradient of

membrane voltage to be zero at boundary condition. Measurements made from a thin strip of tissue with dimensions of  $3 \times 100$  grid points ( $0.75 \times 25$  mm) for restitution, and  $200 \times 200$  ( $50 \times 50$  mm) for studies of re-entry. Action potential duration (APD) and conduction velocity (CV) restitution were measured using an SIS2 protocol with  $S1=1000$  ms, and re-entry was initiated by imposing an Archimedian spiral on the tissue as an initial condition.

### 3. Results

The effect of elevated  $[K^+]_o$  and reduced  $[ATP]_i$  on action potential shape in ORd and TP06 models is illustrated in Figure 1 and 2. The accumulated extracellular potassium was associated with a change in resting potential and a reduction of upstroke velocity of the repolarization phase of AP ( $V_{max}$ ). The results also demonstrate that  $I_{K,ATP}$  activation acted to increase the total outward current during repolarization, resulting in shortened APD (Figure 1 and 2). APD was shortened in both models; however the rate of action potential repolarization in TP06 model is more than ORd model. Figures 3 and 4 show simulated ischaemia acted to shorten APD and flatten APD restitution. The TP06 model APD restitution was steeper in comparison to ORd model.

Reduced  $[ATP]_i$  acted to shorten APD and flatten the APD restitution curve (Figure 3 and 4), but had little effect on CV restitution (Figure 5 and 6). In contrast to the effect of decreased  $[ATP]_i$ , accumulated  $[K^+]_o$  had little effect on APD (Figure 3 and 4), but acted to reduce CV (Figure 5 and 6). The reduced CV can be associated with increased resting potential in tissue with elevated  $[K^+]_o$ . This change is because of a reduction in the magnitude of the inward  $Na^+$  current during depolarisation, which therefore reduces the rate of change of membrane voltage during the action potential upstroke, and hence acts to reduce CV.

Spiral re-entry behavior was simulated in normal and ischemic tissue with a single re-entrant wave as the initial condition. All combinations of  $[ATP]_i$  and  $[K^+]_o$  resulted in stable re-entry. The average period of re-entry for different combinations of  $[ATP]_i$  and  $[K^+]_o$  is summarized in Table 1 and 2. Elevated  $[K^+]_o$  increased the period of re-entry from 220 ms (TP06) and 295 ms (ORd) to around 355 ms. Reduced intracellular  $[ATP]_i$  decreased the period of re-entry to between 150 ms (TP06) and 170 ms (ORd). The period of re-entry was increased resulting from elevated  $[K^+]_o$  due to a reduction in CV and hence decreased activation rate. In contrast, unchanged CV resulting from decreased  $[ATP]_i$  acted to decrease the period of re-entry and thus to increase activation rate. These results were similar in both models. Figures 7 and 8 illustrate a snapshot of

membrane voltage in the 2D tissue sheet after 400 ms of initiation of the spiral wave.

Table 1. Average period of spiral wave re-entry (ms) in simulations with different combinations of  $[ATP]_i$  and  $[K^+]_o$  ORd model.

$[K^+]_o$ (mM)	5.4	6.0	8.0
$[ATP]_i$ (mM)			
6.8	295	300	355
6.0	270	280	335
5.0	215	225	295
4.0	170	175	230

Table 2. Average period of spiral wave re-entry (ms) in simulations with different combinations of  $[ATP]_i$  and  $[K^+]_o$  TP06 model.

$[K^+]_o$ (mM)	5.4	6.0	8.0
$[ATP]_i$ (mM)			
6.8	220	240	310
6.0	210	220	300
5.0	180	200	-
4.0	150	170	-

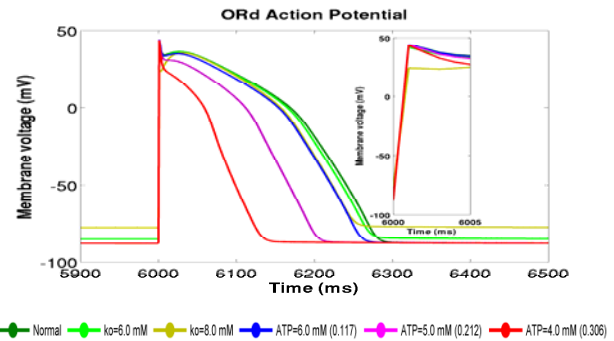


Figure 1. Effect of increased  $[ATP]_i$  and decreased  $[K^+]_o$  on action potential shape in ORd model.

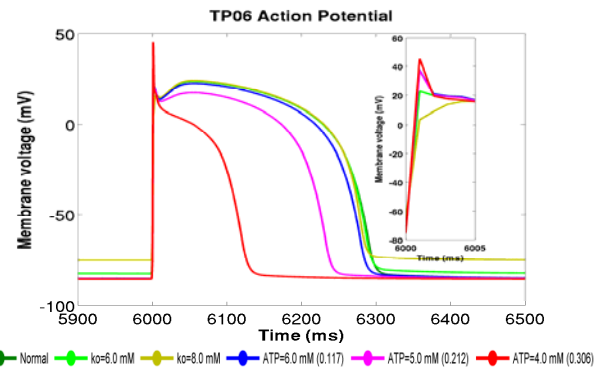


Figure 2. Effect of increased  $[ATP]_i$  and decreased  $[K^+]_o$  on action potential shape in TP06 model.

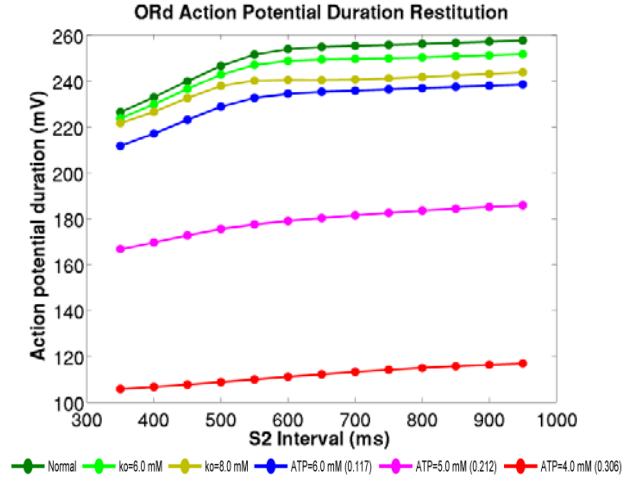


Figure 3. Effect of increased  $[ATP]_i$  and decreased  $[K^+]_o$  on APD restitution in ORd model.

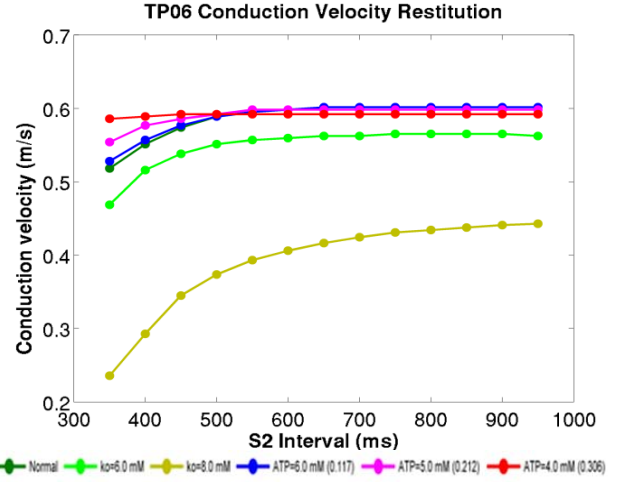


Figure 6. Effect of increased  $[ATP]_i$  and decreased  $[K^+]_o$  on CV restitution TP06 model.

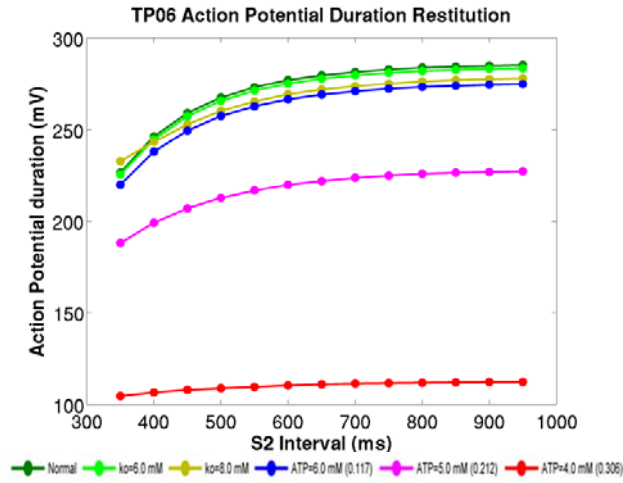


Figure 4. Effect of increased  $[ATP]_i$  and decreased  $[K^+]_o$  on APD restitution in TP06 model.

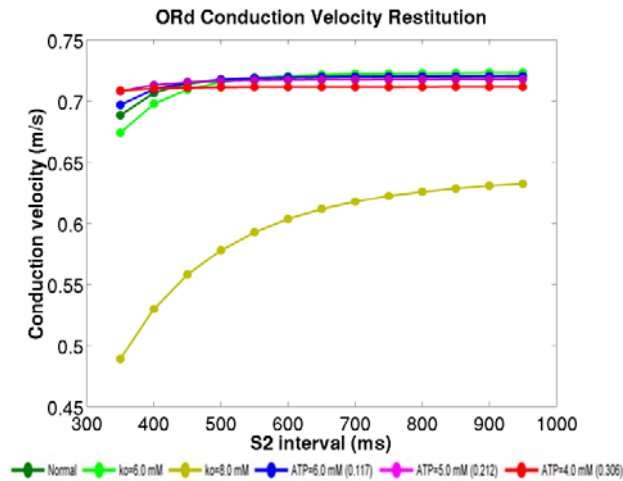


Figure 5. Effect of increased  $[ATP]_i$  and decreased  $[K^+]_o$  on CV restitution in ORd model.

#### 4. Discussion and conclusions

This study compares the dynamical behaviour and impact of simulated global cardiac ischaemia in two cell models (ORd and TP06). We have shown the effects of different components of ischaemia on human ventricular 2D tissue. In both models, reduced  $[ATP]_i$  acted to decrease APD, while elevated  $[K^+]_o$  acted to increase wavelength and hence acted to reduce CV. The change in resting potential resulting from the elevated  $[K^+]_o$  acts to reduce the magnitude of  $I_{Na}$  during depolarization, which reduces  $dV/dt$  during the action potential upstroke (Figures 1 and 2), and thus acts to reduce CV (Figures 5 and 6). The results obtained from both models indicate that simulated ischaemia would act to stabilise re-entry. The flattening of APD restitution from reduced  $[ATP]_i$  and elevated  $[K^+]_o$  would be expected to increase the stability of re-entry in ischaemic tissue. This idea also will be examined by using multiple wavelet re-entry as an initial condition for simulations with reduced  $[ATP]_i$  and elevated  $[K^+]_o$  in our next study.

In our future work, we will extend our 2D simulations into 3D to investigate the contribution of different types of heterogeneity to wavebreak during ventricular fibrillation in the human heart with global myocardial ischaemia.

There are several limitations in this study. First, we have used a formulation of  $I_{K,ATP}$  [5] which is not based on data from human ventricular myocytes. Second, we have not taken into account regional differences in  $[K^+]_o$  and  $I_{K,ATP}$  activation, which are two sources of heterogeneity that could explain the continuing wavebreak in experimental studies, however the tissue geometry and fibre-sheet structure of ventricular wall

could be effective as well as regional differences in the response to ischaemia within the ventricular wall [7].

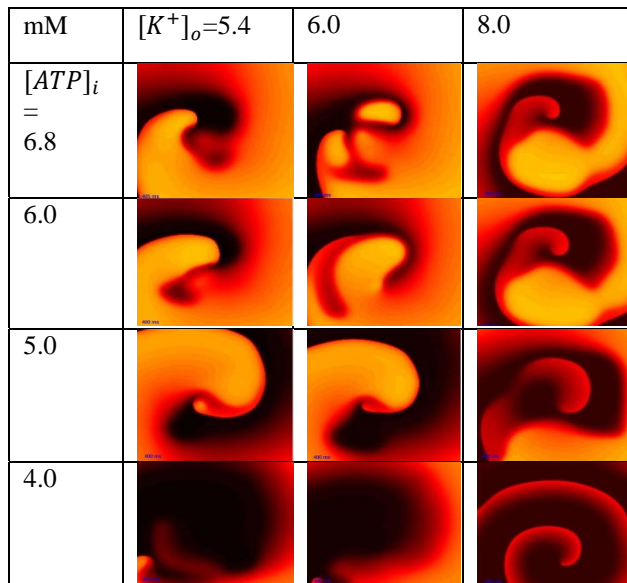


Figure 7. Snapshots of re-entry (ms) in ORd model with different combinations of  $[ATP]_i$  and  $[K^+]_o$ , 400 ms after initiation. Colour intensity shows membrane voltage, with brighter colours indicating more depolarised tissue.

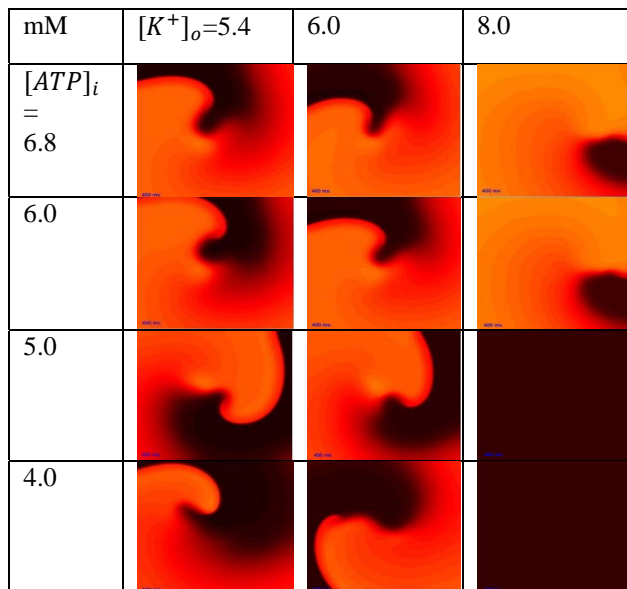


Figure 8. Snapshots of re-entry (ms) in TP06 model with different combinations of  $[ATP]_i$  and  $[K^+]_o$ , 400 ms after initiation.

Finally, in this study, we simulated 2D homogeneous ventricular tissue rather than 3D heterogeneous tissue, like the real heart. Therefore, another important limitation to this study is structural features such as tissue anisotropy, fibre rotation, and complex anatomic structures were not taken into consideration.

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