Re-entry in a Model of Ischaemic Ventricular Tissue

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Abstract

Ventricular fibrillation in the human heart results in global myocardial ischaemia. The aim of this study was to examine how ischaemia modulates the stability and period of re-entry in a computational model of human ventricular tissue. 2D tissue sheets were simulated using the monodomain equation with cellular electrophysiology described by the Ten Tusscher 2006 model. We modeled ischaemia by elevating $[K^+]_o$, reducing GCa_L, and activating the ATP dependent K^+ current. These changes acted to prolong the refractory period of tissue, to reduce conduction velocity, and to flatten restitution. In simulated normal tissue, re-entry had a period of between 230 and 300 ms, whereas in simulated ischaemic tissue the period was prolonged to around 400 ms. Elevating $[K^+]_o$ to 8.0 mM converted unstable re-entry to stable re-entry. The mechanisms that sustain fibrillation in normal and globally ischaemic human ventricular tissue are likely to be different.

1. Introduction

Spontaneous episodes of ventricular fibrillation (VF) result in global myocardial ischaemia, which results in membrane depolarisation, reduced excitability, shortening of action potential duration (APD) and slowed conduction velocity (CV) [1]. These changes act to slow the activation rate of VF [2, 3], and prolonged global ischaemia alters the mechanism sustaining VF [4, 5]. Studies in the isolated myopathic human heart indicate that global cardiac ischaemia followed by reperfusion influences the activation rate and complexity [6].

The aim of this study was to use a computational model of human ventricular tissue to examine the way that ischaemia and reperfusion of cardiac tissue influences APD and CV restitution, and the period and stability of re-entry.

2. Methods

A cardiac tissue model representing a 2D sheet of human ventricular myocyctes was constructed. Two variants of the model were used; in the first variant APD restitution was relatively flat and re-entry was stable, and in the second variant restitution was steep and re-entry was unstable.

2.1. Cell model

The 2006 version of the ten Tusscher Noble Noble Panfilov (TNNP) model of human ventricular myocytes was used. This version has more detailed Ca^{2+} handling [7] compared to the original model [8]. We used the parameters for epicardial cells, and the parameter sets with flat (slope 0.7) and steep (slope 1.8) APD restitution [7] described in Table 1. All other parameters used the values given in the original paper.

Table 1. Parameter set for each tissue model.

Parameter value	Flat restitution	Steep restitution
GK_r	0.153	0.172
GK_s	0.392	0.441
GpCa	0.1238	0.8666
GpK	0.0146	0.00219
tau f	× 1.0	× 2.0

2.2. Tissue model and numerical scheme

We used a monodomain tissue model [9] with isotropic diffusion, a diffusion coefficient of 1.171 $cm^2\ s^{-1}$, and a specific capacitance of 1 $\mu F\ cm^{-2}$. This model was solved using an explicit finite difference scheme with a space step of 0.025 cm, and adaptive time stepping [10] with a time step between 0.02 and 0.2 s. No-flux boundary conditions were imposed at each edge by setting the gradient of membrane voltage to be zero at boundary points. A lookup table with a voltage resolution of 0.1 mV was used to pre-compute all voltage-dependent components of the cell model. The size of the tissue grids were 3 × 50 (0.75 × 12.5 mm) for measurements of restitution, and 600 × 600 (150 × 150 mm) for studies of re-entry. Re-entry was initiated by imposing an Archimedian spiral on the tissue [11], and restitution was

measured using an S1 S2 protocol with six S1 stimuli with a 1000 ms cycle length.

2.3. Ischaemia

In our model of cardiac ischaemia we chose to include the effects of (i) elevated extracellular K^+ concentration, (ii) anoxia resulting in increased intracellular ATP concentration and subsequent activation of an ATP sensitive K^+ current, and (iii) acidosis resulting in reduced magnitude of the L type Ca^{2+} current $I_{Ca,L}$. Other studies have shown that acidosis also influences the Na/Ca exchanger current I_{NaCa}, and the Na current $I_{Na.}$ [12]. Our initial studies indicated that these effects are small, and we did not include these effects in our study.

The elevation in $[K^+]_o$ was simulated by increasing $[K^+]_o$ from its default value of 5.4 mM to 7.0 and 8.0 mM. We added an additional ATP activated K^+ current $I_{K,ATP}$ using the formulation described by Shaw and Rudy [13].

$$I_{K,ATP} = G_{K,ATP} \frac{1}{1+\left(\frac{[ATP]_i}{K_{0.5}}\right)^H} \left(\frac{[K^+]_o}{5.4}\right)^n (V_m - E_K)$$

$G_{K,ATP}$ was the maximum conductance of this current, with a value of 3.9 nS cm^{-2} [13]; $[ATP]_i$ intracellular ATP concentration, with a normal value of 6.8 mM and a value in ischaemic tissue of either 5.5 or 5.0 mM [14]; $K_{0.5}$ had a value of 0.042 for normal tissue, and 0.125 or 0.25 for ischaemic tissue [13]; H a value of 2.0 [13]; and n a value of 0.24. The effect of acidosis was simulated by decreasing the maximum conductance of the L type Ca^{2+} current GCa_L to 90% and 80% of its default value.

The values of $[K^+]_o$, GCa_L, $[ATP]_i$ and $K_{0.5}$ chosen to characterise normal tissue, mild ischaemia, moderate ischaemia, and reperfusion are indicated in Table 2. We assumed that during reperfusion accumulated $[K^+]_o$ is washed out of the tissue quickly, while the other effects take relatively longer to return to baseline values.

Table 2. Model parameters for normal, ischaemic, and reperfused tissue.

	$[K^+]_o$ (mM)	GCa_L (%)	$[ATP]_i$ (mM)	$K_{0.5}$
Normal	5.4	100	6.8	0.042
Mild ischaemia	7.0	90	5.5	0.125
Moderate ischaemia	8.0	80	5.0	0.250
Reperfusion	6.0	90	5.5	0.125

3. Results

The effect of simulated mild and moderate ischaemia, and reperfusion on APD and CV restitution is shown in Figures 1 and 2 for each variant of the model. In each

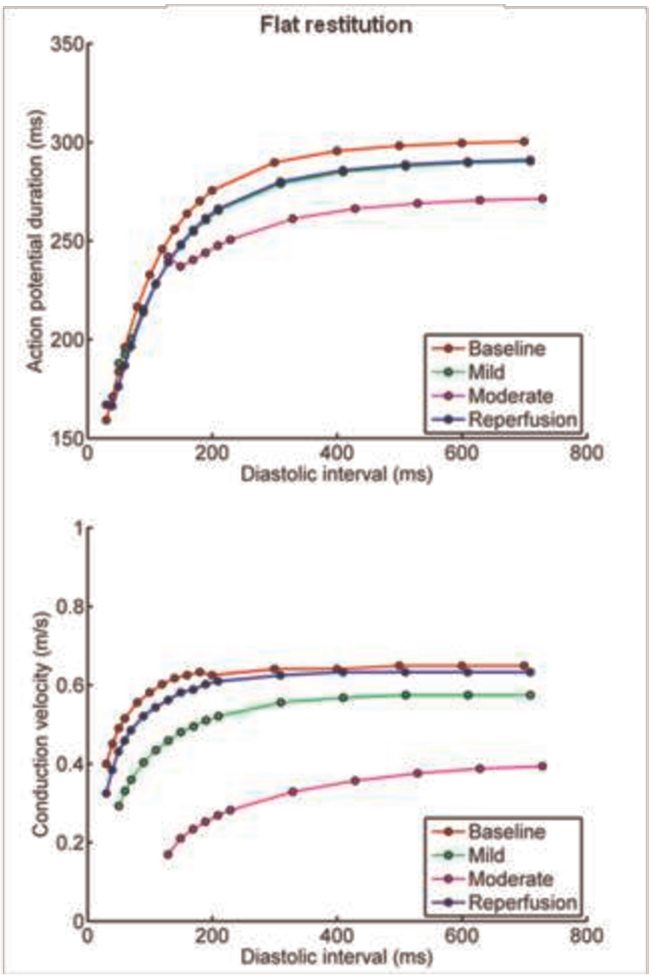

Figure 1. Effect of simulated ischaemia and reperfusion on APD and CV restitution in tissue with flat restitution

case, reducing GCa_L and intracellular ATP concentration acted to reduce APD, whereas increasing $[K^+]_o$ acted to increase refractory period (increasing the minimum diastolic interval at which a propagating action potential could be elicited), and to reduce CV.

In simulated normal tissue, re-entry was stable in the flat restitution variant. In the steep restitution variant, re-entry was unstable, breaking up into multiple wavelets after 3 s simulated activity. In both tissue variants, re-entry was stable with simulated ischaemia and reperfusion (Figures 3 and 4).

When the unstable re-entry generated by the steep restitution variant was used as an initial condition, the effect of moderate ischaemia was to convert unstable re-entry to stable re-entry, whereas with mild ischaemia and reperfusion unstable re-entry persisted (Figure 5).

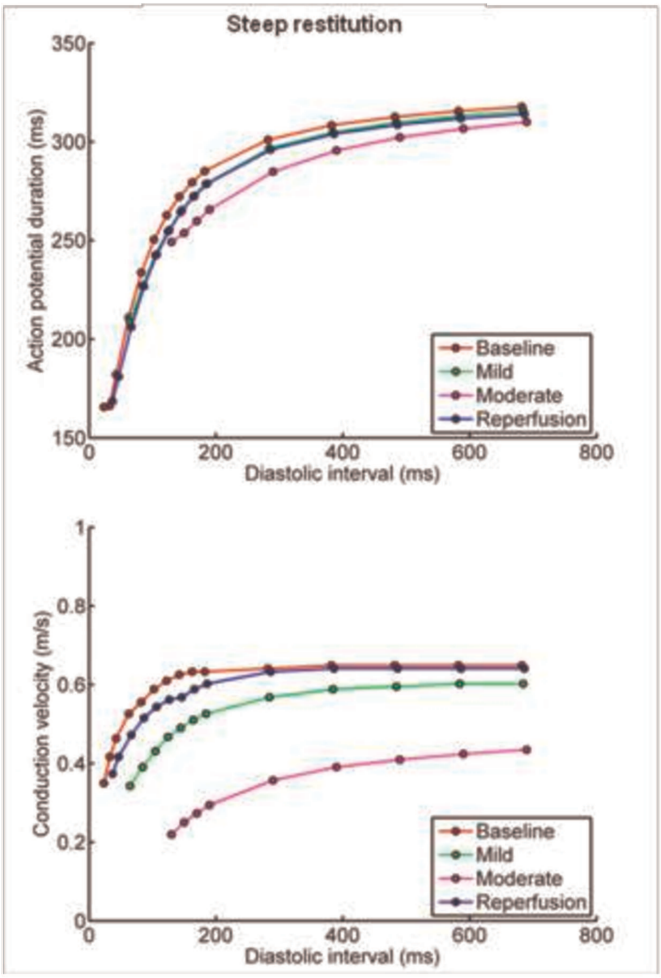

Figure 2. Effect of simulated ischaemia and reperfusion on APD and CV restitution in tissue with steep restitution

4. Discussion and Conclusions

This study indicates the rich varieties of behaviour that can be produced in a cardiac tissue model, when the values of parameters are changed. The parameter changes chosen for this study are representative of the changes that take place in ischaemia, and several potentially important effects have been omitted, including the complexity of real cardiac anatomy, and the effects of ATP changes on Na/Ca exchange and the Na current. Nevertheless, the flattening of restitution curves found in this study is consistent with measurements of restitution in the human heart during ischaemia [15], and the studies in animal hearts where global myocardial ischaemia has been found to reduce the complexity of VF activation patterns [16].

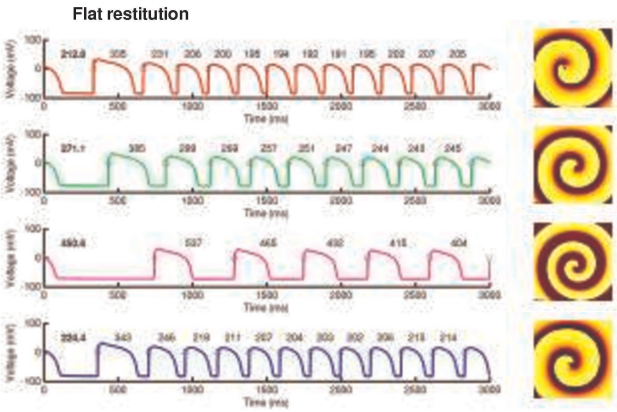

Figure 3. Time series of membrane voltage in tissue with flat restitution showing (top to bottom) normal tissue, mild ischaemia, moderate ischaemia, and reperfusion Numbers indicate the period of re-entry in ms. Snapshots at right show re-entry 3 s after initiation, where brighter colours indicate depolarised tissue.

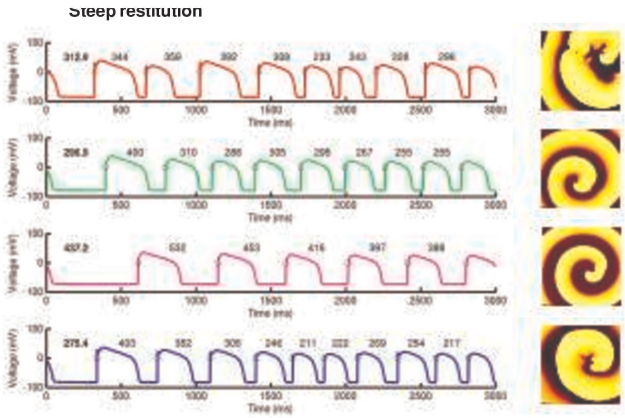

Figure 4. Time series of membrane voltage in tissue with steep restitution showing (top to bottom) normal tissue, mild ischaemia, moderate ischaemia, and reperfusion Numbers indicate the period of re-entry in ms. Snapshots at right show re-entry 3 s after initiation, where brighter colours indicate depolarised tissue.

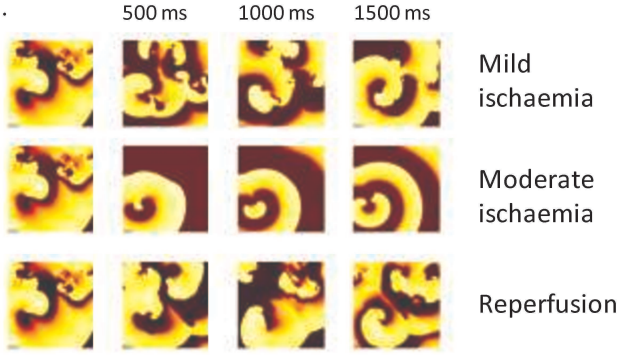

Figure 5 Snapshots of re-entry in tissue with steep restitution where unstable re-entry is used as initial condition.

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