Formulation of ATP sensitive K^+ Current and Action Potential Shape in Models of Human Ventricular Myocytes

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Abstract

The contribution of the ATP-sensitive K^+ (K^+_{ATP}) current to the action potential is an important component of cardiac ischaemia. The purpose of this study was to investigate how the formulation of $I_{K(ATP)}$ influences action potential shape and duration in the Ten Tusscher-Panfilov 2006 model of human ventricular myocytes. We compared four different $I_{K(ATP)}$ formulations, which were inserted in the epicardial variant of the cell model embedded in a 2D monodomain tissue model. The results demonstrate that inserting $I_{K(ATP)}$ in the cell models shortens APD as intracellular ATP concentration is reduced, consistent with experimental findings. Although the current-voltage properties of each $I_{K(ATP)}$ formulation were different, each formulation had a similar effect on the properties of the tissue model.

1. Introduction

Anoxia, reduction of $[ATP]_i$, and activation of $I_{K,ATP}$, is one of the major pathophysiological components of myocardial ischaemia. Experimental evidence [1-3] shows that activation of $I_{K,ATP}$ results in shortening of action potential duration (APD). Several formulations [4-7] of the ATP activated K^+ current $I_{K,ATP}$ have been developed, based on these experimental data.

The main goal of the present study was to use a computer model to quantitatively study the influence of $I_{K,ATP}$ activation on action potential propagation in a 2D tissue model. For this purpose, we compared four different formulations of $I_{K,ATP}$ and have incorporated them into a 2D monodomain tissue model [8]. This model used to study the relationship between APD, conduction velocity (CV) and the ATP activated K^+ current $I_{K,ATP}$.

2. Methods

2.1. Cell model and formulation of $I_{K,ATP}$

We studied three different formulations of the ATP activated K^+ current $I_{K,ATP}$ [4-6] based on animal data, and one formulation [7] based on in vitro experiments in human ventricular myocytes [9]. The formulations of $I_{K,ATP}$ are presented as follows:

1. The Ferrero et al. [4] formulation was implemented described by equation 1, with modifications from the original description described below:

$$I_{K,ATP} = g_0 \left(\frac{[K^+]_0}{5.4}\right)^{0.24} f_{ATP}(V_m - E_k) \quad (1)$$

2. The formulation described by Shaw and Rudy [5]:

$$I_{K,ATP} = G_{K,ATP} \frac{1}{1+\left(\frac{[ATP]_i}{K_{0.5}}\right)^H} \left(\frac{[K^+]_0}{5.4}\right)^n (V_m - E_k) \quad (2)$$

3. The formulation described by Matsuoka et al. [6], which also is based on guinea pig ventricular cell data, was implemented as:

$$I_{K,ATP} = G_{K,ATP} \frac{0.8}{1+\left(\frac{[ATP]_i}{0.1}\right)^2} \left(\frac{[K^+]_0}{6.019\times10^6}\right)^{0.24} (V_m - E_k) \quad (3)$$

4. The formulation described by Kazbahnov et al [7] was implemented as:

$$I_{K,ATP} = Af_{ATP} \left(\frac{[K^+]_0}{5.4}\right)^{0.3} \frac{1}{40+3.5e^{0.025V}} (V_m - E_k) \quad (4)$$

The original Ferrero et al. [4] formulation, which was based on different sets of experimental data for guinea pig, described the dependence of the channel current density on ion concentrations ($[K^+]_0$,$[Mg^{2+}]_i$ and $[Na^+]_i$) and intracellular nucleotide levels ($[ATP]_i$ and $[ADP]_i$) [4]. The modified version of this formulation was used, to be consistent with experimental observations of APD [5-7].

In the Shaw and Rudy [5] and Matsuoka et al. [6] formulations, which also were based on data for guinea-pig ventricular cell, a set of individual parameter values had been assigned to combine the ischaemic conditions. In these formulations $I_{K,ATP}$ activated at $[ATP]_i$ level. However, in the Shaw and Rudy formulation the $K_{0.5}$

parameter was assigned to highlight the possible role of pH dependence of the K(ATP) channel.

In each of these formulations V_m and E_k indicate the membrane voltage and reversal potential for K^+ ions respectively. Extracellular potassium concentration, $[K^+]_0$,was set 5.4 mM. H is a Hill coefficient set to 2.0, and n was set to 0.24 [2]. $G_{K,ATP}$ is the maximum conductance of, $I_{K,ATP}$ set to 3.9 $mS\ mm^{-2}$ and 0.17674 $mS\ mm^{-2}$ for the Shaw and Rudy [5] and Matsuoka et al. [6] formulations respectively. g_0 is the maximum channel conductance in the absence of Na^+, Mg^{2+} and ATP, set to 2.01 $mS\ mm^{-2}$ for epi cell type [10]. f_{ATP}, the fraction of opened channels, was varied between 0% for a normal value $[ATP]_i$ of 6.8 mM and 0.4% for ischaemia [7]. The scaling coefficient A was fitted to the formulation with value of 155 [7]. Anoxia was simulated by reducing $[ATP]_i$ from its normal value of 6.8 mM to 6.0, 5.0, 4.5 and 4.0 mM. The half maximal saturation of $I_{K,ATP}$, $kATP$, was varied between 0.042 mM for a normal $[ATP]_i$ 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, 0.259 for reduced $[ATP]_i$ of 4.5 mM and 0.306 mM for reduced $[ATP]_i$ of 4.0 mM in the Shaw and Rudy [5] formulation.

We used a human ventricular cell model, the Ten Tusscher Panfilov 2006 (TP06) model [8] to represent a human cellular electrophysiology. The parameters have been set for epicardial cells, with modification of the models of K(ATP) current to simulate ischaemia.

2.2. Tissue model and numerical approach

To assign restitution properties, we used a 2D monodomain tissue model [11] with dimensions 3 × 100 grid points (0.75 × 25 mm) embedding the TP06 cell model with isotropic diffusion, a diffusion coefficient of 1.171 $cm^2\ s^{-1}$ (TP06 model), and a specific capacitance of 1 µF cm^{-2} . This model was solved with an explicit finite difference approach with a fixed space step of 0.2 mm. No-flux boundary conditions were imposed at each edge by setting the gradient of membrane voltage to be zero at boundary condition.

2.3. Dynamic properties of the model

To examine the effect of each $I_{K,ATP}$ formulation on the properties of the tissue model, we measured how these models influenced APD and CV restitution. The S1S2 protocol with S1=1000 ms was used to measure action potential duration (APD) and conduction velocity (CV) restitution.

3. Results

3.1. Models of $I_{K(ATP)}$

In the first step, we compared the current-voltage properties of each $I_{K,ATP}$ formulation (Figure 1). In this figure, $I_{K(ATP)}$ is the current through a single fully activated channel. This figure presents the results obtained with the model of the unitary conductance in terms of the current-voltage relationships of the channel. In figure 2, we further explore the slope of voltage dependency of each $I_{K(ATP)}$ model. The result shows the slope of Ferrero and Kazbahnov formulations is almost the same; however there was a big difference in the slope of the Matsuoka et al. formulation compared to other formulations, indicating that this formulation would produce a larger outward current for a given level of activation.

Several experimental studies [1-3] support the idea that $I_{K,ATP}$ channel activation largely accounts to the changes in APD resulting from the activation of any outward current or the decline of any inward current [4]. Our results also illustrated that a fall in in $[ATP]_i$ is responsible for action potential shortening through activation of K,ATP channels.

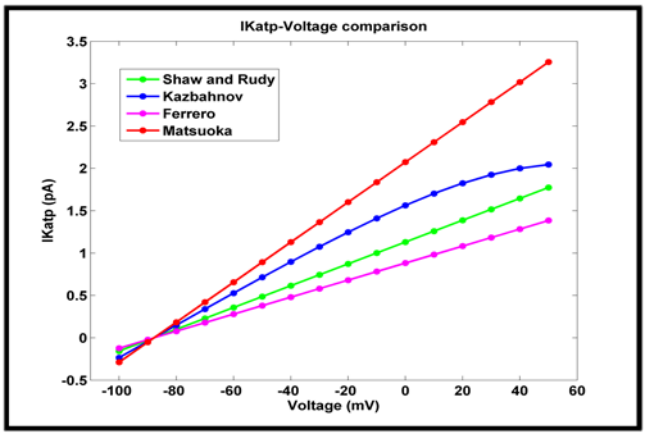

Figure 1. Current-voltage dependency for the KATP current in four different models.

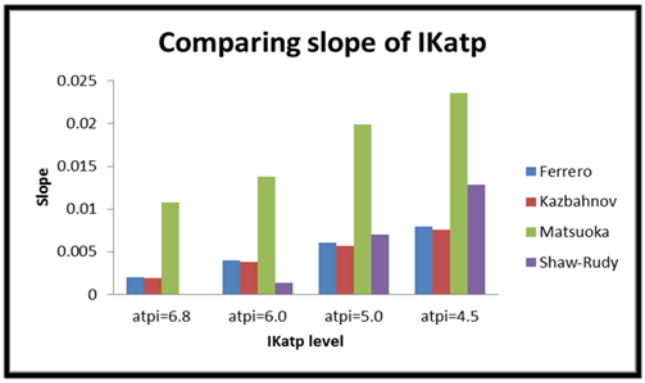

Figure 2. Comparison the slope of $I_{K(ATP)}$-voltage in four different models.

3.2. Influence of $I_{K,ATP}$ on action potential duration

Activation of $I_{K,ATP}$ provides an additional outward current during repolarization, and so acts to shorten action potential duration (APD). We examined how different formulations of $I_{K,ATP}$ affect main dynamical characteristic of cardiac tissue, which are a key factor in the stability of cardiac arrhythmias. Figure 3 and 4 show how action potential shape changes with activation of $I_{K,ATP}$. We differentiated the electrophysiological effects of the four different formulations of $I_{K,ATP}$ in figures 3 and 4. Figure 5 shows how APD depends on $I_{K(ATP)}$. This figure shows APD becomes shorter since hypoxia activates a strong depolarizing current. Our results show that the value of CV varied by <0.01 ms with $I_{K(ATP)}$ activation.

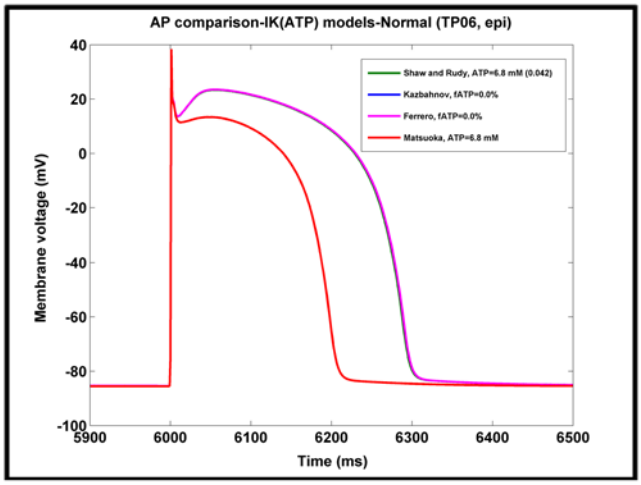

Figure 3. AP morphology for different $I_{K(ATP)}$ formulations with normal $[ATP]_i$ of 6.8 mM.

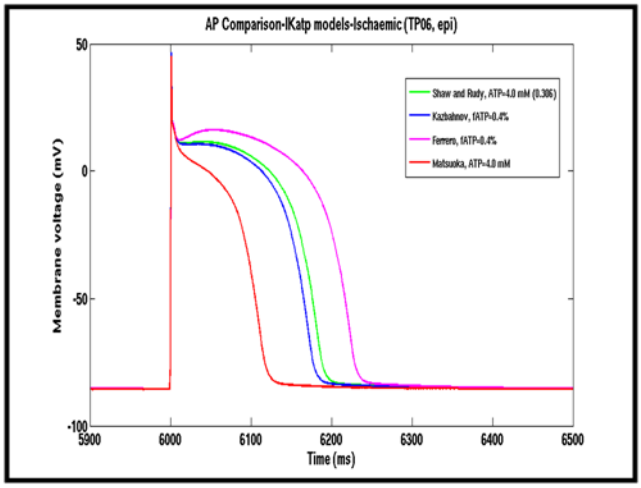

Figure 4. AP morphology for different $I_{K(ATP)}$ formulations, with $[ATP]_i$ decreased to 4.0 mM .

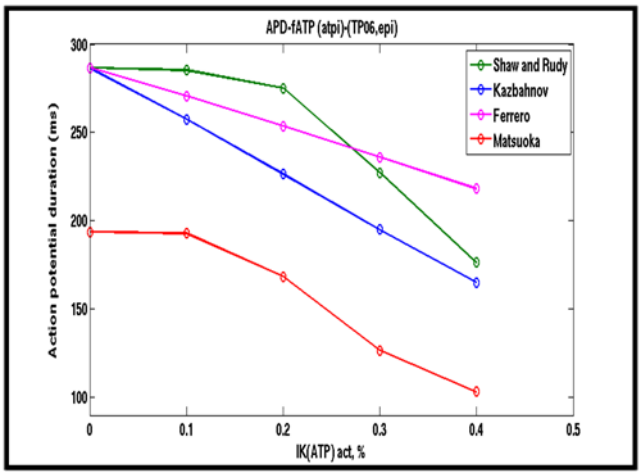

Figure 5. The changes in action potential duration under different $I_{K,ATP}$ activation.

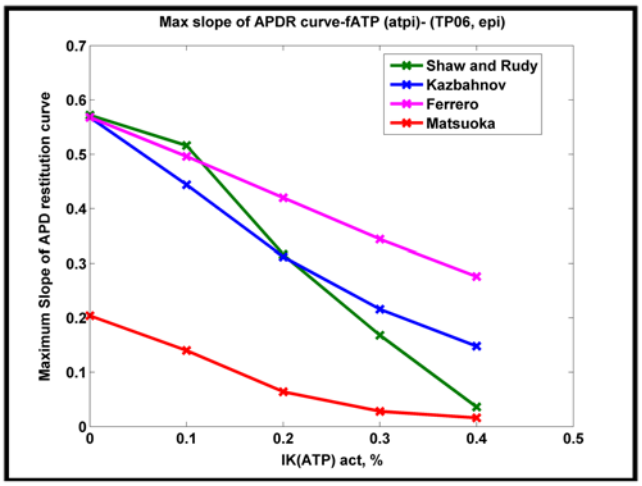

Figure 6. The changes in the maximum slope of APD restitution curves under different $I_{K,ATP}$ activation.

4. Discussion and conclusions

To determine the impact of anoxia on cardiac cell electrophysiology, we compared different formulations of $I_{K,ATP}$. The aim was to evaluate the quantitative influence of three $I_{K(ATP)}$ models, which are based on animal data, and one $I_{K(ATP)}$ model, based on human data. For this purpose, we computed I-V dependence of each model without the conditions of elevated $[K^+]_0$ (Figure 1). Activation of the Matsuoka et al. model, with the biggest slope in I-V curve, had the largest effect on AP shape and the produced a shorter APD in comparison to the rest of models, even with normal levels of $[ATP]_i$. Although the slope of I-V curve (Figure 2) was similar in both Ferrero et al. and Kazbahnov et al. models, the flattening of the APD restitution slope with $I_{K,ATP}$ in the Kazbahnov et al. model was greater in comparison to the Ferrero et al.

model (Figure 6). As shown in figures 5 and 6, the addition of $I_{K,ATP}$ has the biggest effect for the Matsuoka et al. model compared to the Shaw and Rudy formulations. This is because of changing $K_{0.5}$ parameter in the Shaw and Rudy formulation, emphasizing the possible role of pH dependence of the K(ATP) channel. Although a cause and effect relationship between the metabolic and ionic conditions of ischemia and the ischemic electrical changes lies in the complicated interrelationships between events (acidosis, hyperkalaemia), we attempted to differentiate the electrophysiologic effects of the four different $I_{K(ATP)}$ models. The characteristics of APD shortening resulting from $I_{K(ATP)}$ activation in our simulations was similar to the results presented in experimental studies [1-3].

In our future work, we will investigate the contribution of different $I_{K(ATP)}$ models into our 2D and 3D tissue models with different types of heterogeneity to study wavebreak during ventricular fibrillation in the human heart with global myocardial ischaemia.

Finally, our results support the major role of $I_{K(ATP)}$ in the reduction of APD, and flattening of APD restitution as intracellular ATP concentration is reduced. Despite different formulations of $I_{K(ATP)}$, based on either data from human or animal ventricular myocytes, the dynamical behaviour and the response to simulated ischaemia in these models was similar.

The similarity of the simulated electrical behavior observed, by using all $I_{K,ATP}$ models presented in this study, supports the hypothesis that $I_{K,ATP}$ is a major current responsible for action potential duration shortening during acute ischemia. However, the theoretical simulations are not an exhaustive representation of all ischemic conditions. Thus, we cannot certainly propose the most appropriate $I_{K,ATP}$ model for use in simulations of ischaemia, because several conditions are not included that either their effects require further experimental characterization or their presence is not relevant during ischemia. For example, the effect of acidosis on the cardiac potassium current is neglected in these formulations. The possibility of the role of intracellular calcium, rise in $[Ca]_i$ is coincident with the secondary phase of $[K^+]_0$ rise and rapid depletion of $[ATP]_i$, to electrical abnormalities associated with Ischaemia is not included [5].

Acknowledgements

The authors are grateful to ICEBERG, the Linux based High Performance Computing Cluster at Sheffield University.

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