Adaptation of an Action Potential Minimal Model to Acute Ischemia

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Abstract

Simplified action potential "minimal" models, whilst not being able to explain the ionic mechanisms of cardiac action potential, can be useful for cardiac simulation purposes if the model possesses certain basic properties. In this work, we have analyzed one of these "minimal models" (the Bueno model) to investigate its ability to simulate ischemia. We modified the model by adding a new ischemic outward current and changing the fast inward current inactivation gate. The results show that the typical action potential shortening in ischemia is properly simulated, while the ischemic peak membrane potential decrease, the resting potential increase and post-repolarization refractoriness are qualitatively, but not quantitatively, reproduced. However, peak decrease and resting potential increase can be achieved by a further simple model modification. In conclusion, the "ischemic" behaviour of the model makes it suitable for simulations in which refractoriness is not a key factor.

1. Introduction

Dynamic, last generation action potential (AP) models, such as the Ten Tusscher model [1,2] or the Rudy models [3,4], are capable of reproducing normal and pathological (e.g. ischemic) APs with a high degree of electrophysiological detail. However, they can become extremely computationally expensive when used in large scale simulations (i.e. when simulating the electrical activity of a 3D geometrically realistic heart). Conversely, phenomenological ("minimal") models of cardiac AP (e.g. the Fenton-Karma model [5]) are less realistic but also less mathematically complex, thus resulting in much faster simulations when used in a 3D virtual heart.

However, the electrophysiological simplifications inherent to these models (e.g. the non-existence of individual realistic ionic currents) jeopardizes their usefulness to simulate cardiac pathologies. Ischemia, for instance, is a complex phenomenon which implies the modification of channel conductances, ionic concentrations and inter-cellular resistance. In order to correctly simulate ischemia, these models would need certain modifications which would have to maintain simplicity while reproducing the basic features of ischemia.

The Bueno model [6,7] is a "minimal" model based on the Fenton-Karma equations [5]. In its original form, it describes the cardiac AP as a result of the interaction of three currents termed "fast inward" current (I_{fi}), "slow inward" current (I_{si}), and "slow outward" current (I_{so}), which approximately represent the fast sodium inward current, the delayed inward calcium currents and the different potassium outward currents, respectively. It reproduces the human cardiac AP waveform for endocardial, epicardial and midmyocardial cells with great accurateness, and it also correctly mimics the different APD restitution curves. Although it has been used to simulate pathologies such as the Brugada syndrome [7], it was not intended to simulate acute myocardial ischemia.

The aim of this work is to investigate the validity of the Bueno model to reproduce myocardial ischemia at the cellular level.

2. Methods

In order to try to reproduce the ischemic behavior of cardiac myocytes, we modified the Bueno model [6] in two ways. First, we introduced a new outward current termed "slow outward ischemic" current (I_{soi}), which approximately represents the ATP-sensitive potassium current ($I_{K(ATP)}$) [8] which activates in hypoxia (and thus in acute ischemia) and is responsible for action potential duration (APD) reduction [9]. Said current was formulated as

$$I_{soi} = g_{soi}\left(u - E_{soi}\right) \qquad [1]$$

where g_{soi} is the total voltage-independent conductance associated to the current (mimicking the K(ATP) conductance), u is membrane potential (as defined in the Bueno model) and E_{soi} is a voltage-independent term

which mimics the effect of the potassium Nernst potential (which increases - becomes less negative - during the ischemia-induced hyperkalemia).

Second, we changed the formulation of the v gate in the Bueno model [6]. In the original model, this gate is formulated following the Hodgkin-Huxley formalism with a steady-state function v_∞ which follows a Heaviside-type formulation (1 if $u < u_q$, 0 if $u \geq u_q$). We modified the formulation of v_∞ as follows:

$$v_\infty = \frac{1}{1 + \left(u/u_q\right)^2} \qquad [2]$$

In this way, it would be expected that the increment in resting membrane potential potentially caused by the activation of the slow outward ischemic current would reduce the resting value of v_∞, which in turn would help developing post-repolarization refractoriness, a key feature of ischemia [10,11].

The model for a single cell was implemented in Matlab. Measurements were taken in the tenth AP elicited by a train of stimuli with a frequency of 0.5 Hz. A 200-cell strand was also implemented for refractory period measurements.

3. Results

In normoxic conditions ($g_{soi} = 0$), the modifications did not exert significant changes in the AP waveform, except for a slight prolongation of APD (less than 5 milliseconds, not shown). Figure 1 shows AP waveforms for different values of g_{soi}, both for endocardial cells (Panel A) and epicardial cells (panel B). As expected, APD duration decreases as g_{soi} progresses from its normoxic value ($g_{soi} = 0$) to higher values. In the case of the endocardial cell, $g_{soi} = 0.35$ reduces APD to 50%, which approximately corresponds to the first 10 minutes of acute ischemia [9,11]. In the epicardial cell, this is achieved with $g_{soi} = 0.48$. Thus, AP shortening in ischemia is well reproduced by the modified model.

A sensitivity study was then performed to characterize the behaviour of the model for different values of g_{soi} and E_{soi}. Figure 2 graphically shows the results of this study. Horizontal axis shows the value of E_{soi}, while each curve corresponds to different values of g_{soi}. In panel A, APD is shown to decrease both with g_{soi} and E_{soi} , something which was expected and which corresponds to experimental results in hypoxia, hyperkalemia and ischemia. Peak membrane potential (not shown) follows the same trend, which is also consistent with how real cells behave, although in this case the degree of peak AP reduction is very low (only 1%), which does not correspond to the much higher values (≈ 20%) found experimentally. Finally, panel B shows how resting membrane potential increases with E_{soi} (i.e. with hyperkalemia) and only slightly with g_{soi} (i.e. with hypoxia), which again is correct except for the values of the increase. Membrane potential in the Bueno model is a dimensionless parameter, but a comparison in terms of percentage reveals that the equivalent diastolic depolarization of the ischemic cell is well below the experimental values. Again, the qualitative effect is reproduced, but not the quantitative one.

In order to enhance the peak AP reduction and the resting potential increase, we further increased both g_{soi} and E_{soi}. However, higher values of these parameters yielded unrealistically low values of APD and were therefore disregarded.

We then carried out "dynamic" simulations, in which the ischemic parameters g_{soi} and E_{soi} were increased in a coupled manner to mimic the time-course of acute ischemia. E_{soi} was first increased and then stabilized, simulating the biphasic increase of extracellular potassium in real ischemic cells. Conversely, g_{soi} was linearly increased, as dictated by the real continuous decrease of ATP levels in the acute phase of ischemia. Eventually, both parameters reached values that represented the end of the acute phase of ischemia (approximately 10 minutes after its onset).

The results depicted in Figure 3 show that the three parameters under study (APD, AP peak and resting potential) follow realistic time-courses. Again, APD values seem correct, but not the relative values of the other two.

Finally, Effective Refractory Period (ERP) values were measured in a linear strand which was stimulated in the central cell. The ERP was defined as the minimum coupling interval which resulted in an AP safely propagating along the strand. The results, depicted in Figure 4, show that ERP decreases at a similar rate to APD during the simulated dynamic ischemia. This does not correspond to the real behaviour of ischemic tissue, in which ERP first decreases and then increases well beyond APD (which monotonically decreases) [10]. Post-repolarization refractoriness, which is defined as the difference between ERP and APD, only slightly (and non-significantly) increases during ischemia.

4. Discussion and conclusions

The results obtained with the modified Bueno model indicate that some key features of ischemia can be represented by such simple model, but not others. In particular, APD reduction, which has enormous arrhythmogenesis implications, is correctly represented. However, other ischemic characteristics are not properly

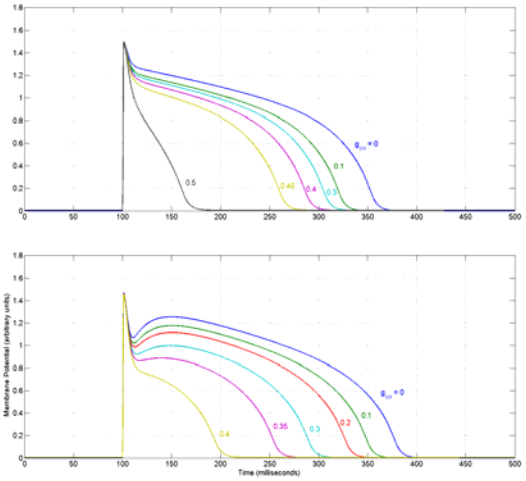

Figure 1. Action potentials obtained with the Bueno model for different values of g_{soi}. A: endocardial action potentials. B: epicardial action potentials.

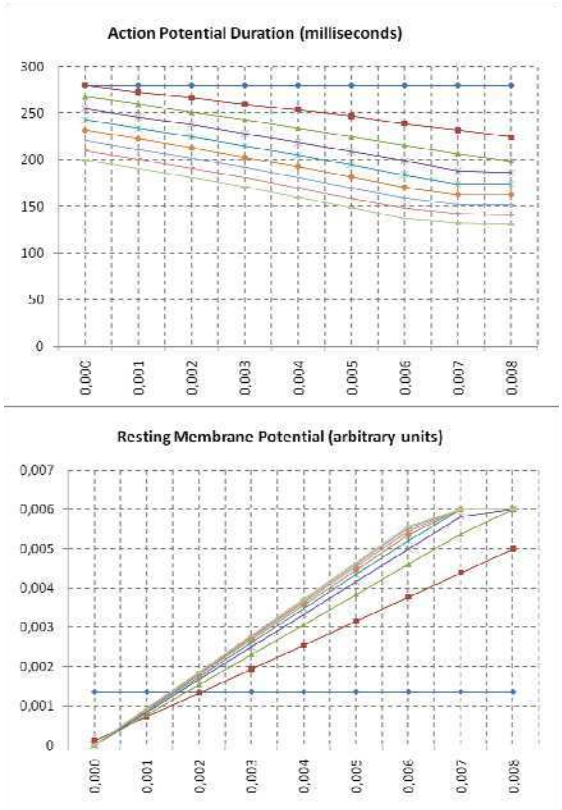

Figure 2. Results of the sensitivity analysis for the ischemic model parameters. A: APD_{90} for different combinations of E_{soi} and g_{soi}. B: Resting membrane potential.

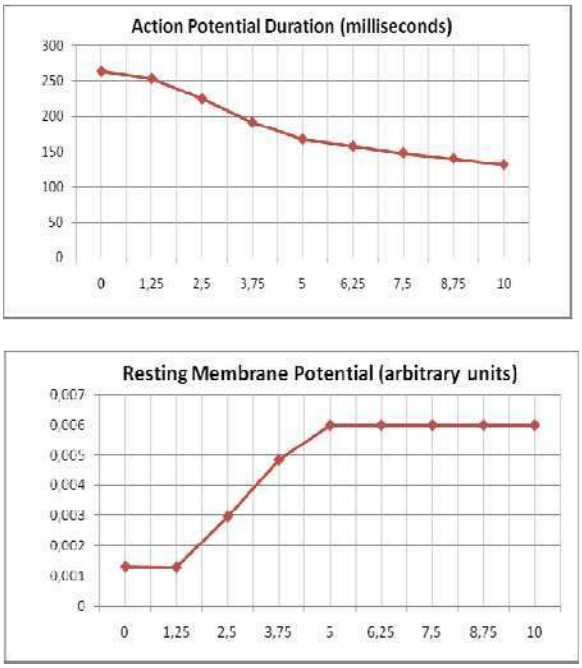

Figure 3. Time course of APD (upper panel) and resting membrane potential (lower panel) during the acute phase of myocardial ischemia. Numbers in the horizontal axis indicate minute after the onset of ischemia.

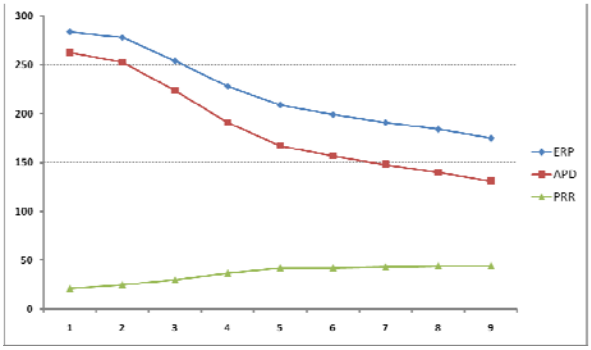

Figure 4. Time course of ERP (upper trace), APD (middle trace) and post-repolarization refractoriness (PRR, lower trace) during the acute phase of myocardial ischemia. Numbers in the horizontal axis indicate minute after the onset of ischemia.

simulated. Among them, the lack of accuracy in reproducing post-repolarization refractoriness jeopardizes the validity of the model in arrhythmia simulations during situations in which cell excitability is a key factor (e.g. in reentry simulations).

The lack of correspondence between the simulated and the experimentally obtained equivalent values for resting potential and peak potential could be surpassed by re-scaling the membrane potential values given by the model. The u parameter representing potential is dimensionless, and a new variable V_m with the dimensions of an electrical potential could be defined by multiplying u by a certain factor (which would depend on the degree of ischemia, and would decrease with time during the acute phase) which would control the peak potential, and by subsequently adding an "offset" potential which would also depend on the degree of ischemia and would account for the progressive diastolic depolarization. However, although appropriate values of said parameters could be found to nicely quantitatively reproduce the waveform of the AP, it would not solve the lack of accuracy of the model in reproducing refractoriness correctly.

In conclusion, the Bueno model is capable of correctly reproducing the ischemic changes in action potential morphology but not changes in excitability, which makes it useful for reproducing non reentrant electrical activity in 3D virtual ischemic hearts.

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References

[1] Ten Tusscher KH, et al., "A model for human ventricular tissue", Am J Physiol Heart Circ Physiol. 2004 Apr; 286 (4):H1573-89.

[2] Ten Tusscher KH, Panfilov AV., "Alternans and spiral break up in a human ventricular tissue model", Am J Physiol Heart Circ Physiol. 2006 Sep;291(3):H1088-100.

[3] Luo CH, Rudy Y., "A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes", Circ Res. 1994 Jun;74(6): 1071-96.

[4] Clancy CE, Rudy Y., "Linking a genetic defect to its cellular phenotype in a cardiac arrhythmia.", Nature. 1999 Aug 5;400(6744):566-9.

[5] Fenton F, Karma A., "Vortex dynamics in three-dimensional continuous myocardium with fiber rotation: Filament instability and fibrillation.", Chaos. 1998 Mar;8 (1):20-47.

[6] Bueno A., "Mathematical modeling and spectral simulation of genetic diseases in the human heart", PhD Dissertation, Ciudad Real, Spain, 2007.

[7] Bueno A., et al, "A model for human ventricular action potentials: Insights into Brugada Syndrome mechanisms", SIAM Conference on Applications of Dynamical Systems, Snowbird (Utah), U.S.A. (May 2005).

[8] Noma A., "ATP-regulated K+ channels in cardiac muscle", Nature. 1983 Sep 8-14;305(5930):147-8.

[9] Ferrero JM Jr, et al, "Simulation of action potentials from metabolically impaired cardiac myocytes. Role of ATP-sensitive K+ current", Circ Res. 1996 Aug;79(2):208-21.

[10] Downar E, Janse MJ, Durrer D., "The effect of "ischemic" blood on transmembrane potentials of normal porcine ventricular myocardium", Circulation. 1977 Mar; 55 (3): 455-62.

[11] Trenor B., et al, "Vulnerability to reentry in a regionally ischemic tissue: a simulation study", Ann Biomed Eng. 2007 Oct;35(10):1756-70.

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