Analysis of the Use of the BPS Model to Simulate Ischemia-induced Hyperkalemia

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Abstract

This study is aimed to test the ability of Bartolucci-Passini-Severi (BPS) model to reproduce the ischemia-induced hyperkalemia, a characteristic feature of the acutely ischemic heart disease. The BPS model is an action potential model of ventricular cardiomyocytes, which correctly reproduces the physiological APD-$[Ca^{2+}]_e$ dependence. The simulations consisted of a 30-minutes progressive ischemic period on an isolated cardiomyocyte. In the simulations hyperkalemia was monitored alongside other variables, including ionic currents, potassium fluxes and concentrations. The simulations revealed that, from the onset of ischemia till the 4.4th minute post-occlusion, the extracellular potassium time course is in agreement with other models. However, after this time point the model shows some discrepancies compared to experimental values. The results demonstrated that at this point the sarcoplasmic calcium release suddenly interrupts which could be related to the failure of opening and closing gates of Ryanodine receptors (RyR).

1. Introduction

Coronary artery disease (CAD) stands as the foremost cause of mortality in the industrialized world, contributing to one in eight global deaths. Myocardial ischemia, a hallmark of CAD, induces profound ionic and biochemical alterations, creating an electrically unstable substrate that can initiate and sustain arrhythmias. The intricate interplay of extracellular changes, such as elevated potassium, Lysophosphatidilcholine (LPC), and adenosine concentrations, alongside intracellular alterations like acidosis and ion concentrations, significantly modifies the transmembrane ionic current fluxes. These modifications result in various disruptions to the myocyte's resting and AP characteristics, leading to hyperkalemia. The term hyperkalemia refers to the increase in extracellular potassium concentration ($[K^+]_e$). A few seconds after the occlusion, $[K^+]_e$ begins to rise, reaching a plateau or experiencing a minor decline approximately 5–10 min after the onset of ischemia. After the plateau phase, a secondary rise in $[K^+]_e$ occurs. Interestingly, this triphasic pattern has been observed in different animal models [1,2,3,4], under different stimulation frequencies [4,5].

LPC, a product of hydrolysis of the phospholipid degradation and its accumulation in the myocardium can be associated with development of the ventricular arrhythmias, introducing some changes in the AP. In the study conducted by Daleau et al., it has been shown that within 10 minutes of ischemia LPC level can increase two or three-fold [6].

As published by Terkildsen et al. in the early stages of simulated ischemia in guinea pig cardiomyocytes, there is a rapid decline in Na^+/K^+ pump amplitude, reaching approximately 65% of the normoxic pump current. This inhibition is primarily due to the decrease in intracellular ATP concentration [7].

The decline in ATP concentration, along with the effects of inorganic phosphate (P_i) and intracellular pH (pH_i), restrains pump activity. However, this inhibition is partially offset by the stimulatory effects of intracellular sodium $[Na^+]_i$ and extracellular potassium $[K^+]_e$ accumulation. Additionally, the decrease in ADP concentration during this phase has a reactivating effect on the pump [7].

Results from different studies showed that the pH_i level immediately after the onset of the ischemia decreases progressively [8].

Because ischemia-induced hyperkalemia is proarrhythmic, and since its intimate causes are not completely understood [1-4, 10], its study using computational models is of interest. Previous studies [10] have shown that the AP model from O'Hara et al. (ORd) [11] is capable of reproducing hyperkalemia. This work aims to test the ability of the newer BPS model [9] to simulate ischemia-induced hyperkalemia.

2. Methods

In this work, the BPS AP model (2020) [9], was utilized to study ischemia-induced hyperkalemia. This model is

basically an improved version of the ORd model. The novelty of BPS model is in considering dynamic electrolyte concentration while other AP models neglect their importance. This novelty enabled the BPS model to reproduce the inverse physiological dependence of APD vs $[Ca^{2+}]_e$. To reach this aim, some ionic current equations were modified. For instance, the L-type calcium current (I_{CaL}), the rapid delayed rectifier (I_{Kr}) and the formulations regarding the calcium release from sarcoplasmic reticulum were modified with respect to the ORd model. Thanks to all the modifications, the physiological APD-$[Ca^{2+}]_e$ dependence was achieved.

To test the ability of BPS model to replicate ischemia-induced hyperkalemia, the ischemic equations were implemented into the model. For this purpose, we used the ischemic equations by Ferrero et al (2023) [10] on the ORd model [11]. The ischemic parameters are composed of the dynamic changes of the metabolites in the cardiomyocyte, which directly play a role in modifying some specific transmembrane currents, ionic pumps and exchangers. Among them, acidosis affects L-type calcium current (I_{CaL}), sodium current (I_{Na}), late sodium current (I_{NaL}), sodium calcium exchanger (NCX) and sodium potassium pump (I_{NaK}). Moreover, the functionality of some pumps and exchangers are also affected by the intracellular ATP and ADP levels in the cell.

To track the dynamics of $[K^+]_e$, the equation below was added to BPS model:

$$\frac{d[K^+]_e}{dt} = \frac{A_s}{V_o F}\sum I_{Kj} + \frac{[K^+]_e - [K^+]_{e,bulk}}{\tau_{ke}}$$

The simulations were carried out in MATLAB 2022b and it consisted of the 35-minutes in total. The first 5-minutes correspond to normoxia and the following 30-minutes replicate progressive acute ischemia. All the simulations were done on the single isolated cell level stimulated at 1Hz.

During this period, also the dynamic changes of metabolites were simulated. Among them, our focus was on the intracellular and extracellular acidosis (pH_i, pH_o), intracellular adenosine levels (ATP_i, ADP_i) and intracellular LPC level. The normoxic values of these parameters were taken from experimental values. For $[ATP]_i$, the normoxic value was set to 10 mmol/L. pH_o was set to 7.4 and pH_i was set to 7.2 [8]. The normoxic value of LPC was assumed 2 µmol/L then, its concentration at 30 minutes after onset of ischemia was estimated to 20 µmol/L [6,12]. The initial value of the $[K^+]_e$ was set to 5.4 mmol/L.

To validate the accuracy and reliability of the results obtained with the BPS model, two strategies were adapted. Firstly, comparison of the results with the gold standard, the ORd model. Secondly, comparison with the experimental values specifically in the case of the $[K^+]_e$ and APD.

3. Results

Following the implementation of the ischemic parameters, initial simulations with the BPS model revealed different characteristics of the APs compared to the ORd model. The normoxic AP analysis of the two models showed some differences. However, the main features showed strong similarities. The APD obtained with the BPS model was slightly shorter than the ORd one. Moreover, the amplitude of the BPS model was higher compared to ORd. Furthermore, it is evident that after the 5th minute of the simulation of acute ischemia the resting membrane potential rises and the APD and amplitude vary, while for the ORd model after 5th minutes of acute ischemia basically the APs are subthreshold.

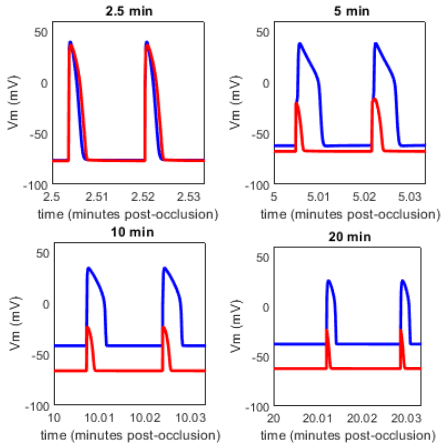

Figure1.Time course of two consecutive APs in different time points of the simulation obtained by BPS (blue) and ORd (red) models.

3.1 Extracellular Potassium

Regarding the ability of the model to simulate ischemia-induced hyperkalemia, the results showed a different time course of [K+]e when compared to the ORd model. Based on the behaviour of the gold standard and in vivo experiments, which were done on animal models, it is expected that during the first 5 minutes of the acute ischemia the [K+]e rises and reaches a plateau level, after which it again increases. However, this behaviour of the BPS model is completely different after the 5th minute of acute ischemia. The BPS model continues to extrude potassium after the 5th minute post-occlusion intensively and reaches approximately 27 mmol/L in the 10th minute, while the ORd plateaus at 12 mmol/L. Meanwhile, the ORd model remains at the plateau level, the extrusion of the K+ ions by BPS model continues with a less sharp trend and peaks at 35mmol/L followed by a slight decrease. Thus, the expected triphasic behaviour is observed in the

BPS model but with unrealistic values (Figure 2).

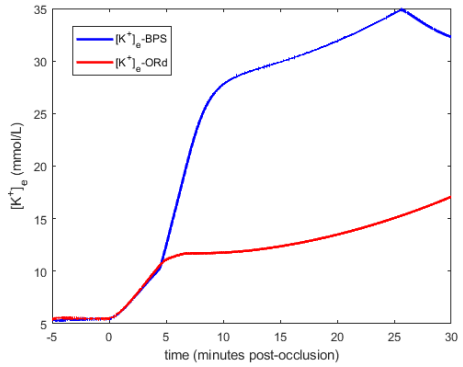

Figure 2. Time course of extracellular potassium in the simulated isolated cardiomyocyte exposed to 30 minutes of acute ischemia using the BPS (blue) and ORd (red) models.

To understand the behaviour of the BPS model when representing ischemia-induced hyperkalemia, the AP and the calcium handling of the cell were monitored.

3.2. Action Potential Analysis

In-depth analysis of the duration of the AP at 90% of repolarization (APD_{90}) revealed more details. One of the stunning properties of the BPS model is its ability for simulating DADs. In the simulation of the acute ischemia, the appearance of the first DAD occurred at the 4.4th minute post-occlusion and the following APs showed an abnormal prolongation. This event could provoke an increase in the outward K^+ flux through the plateau activated currents, namely ATP dependent potassium current (I_{KATP}), slow delayed rectifier (I_{Ks}) and the fast delayed rectifier (I_{Kr}). Normally, the extrusion of K^+ ions through I_{Ks} and I_{Kr} channels is concomitant with the entrance of Ca^{2+} ions through the I_{CaL} current. In our case, the elevation in $[K^+]_e$ caused the elevation of membrane potential towards more positive potentials as it was shown in Figure 1.

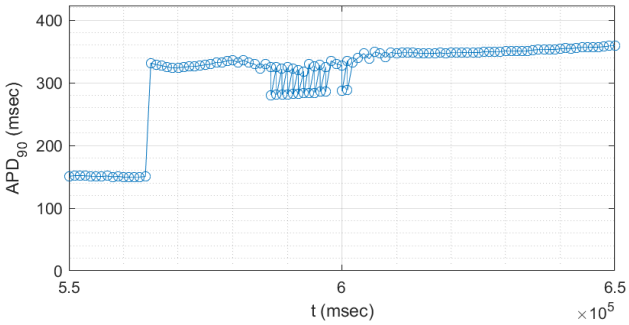

Figure 3. APD_{90} vs time at the time instant of appearance of first DAD at 4.4th minute of simulation.

3.3. Calcium Handling

Intracellular calcium concentration in different cell compartments, namely inside the cell, subspace and inside the sarcoplasmic reticulum, was monitored. The time course of $[Ca^{2+}]$ in the subspace revealed that at the same time instant after appearance of the DAD, calcium concentration went to zero. Conversely, inside the sarcoplasmic reticulum an overload of calcium was observed. To understand what happened to $[Ca^{2+}]$ in the subspace, it is evident that two elements play a role in bringing Ca^{2+} ions to the subspace. Firstly, the calcium release from sarcoplasmic reticulum. Secondly, the I_{CaL} current. Among these two currents, the sarcoplasmic calcium release could justify the observed behaviour since at the corresponding time point it went to zero almost immediately after the first DAD (Figure 4). Thus, all the evidences proved that the extensive extrusion of the K^+ ions after 5th minute of simulation of acute ischemia was associated with the interruption of the calcium-induced calcium release (CICR) process. This event introduced a lengthening in the subsequent APs.

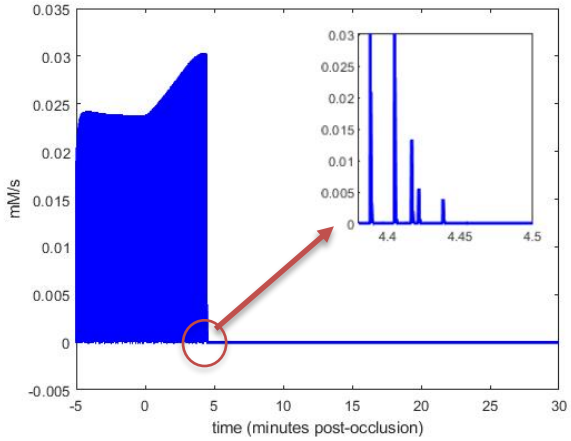

Figure 4. The Interrupted CICR just before 5th minute of simulated acute ischemia. In the zoomed part the premature pulsations are evident.

3.4 Adaptation gate tuning

To address the malfunctioning of gates, the steady-state behavior of the adaptation gate, opening and closing gates of the RyR channels were examined. The proper functioning of the opening and closing gates was critically dependent on the adaptation gate and it is controlled by two key elements: a minimum value and a maximum value. These values set the boundaries for the gate's responsiveness. Initial visualizations of the calcium concentration in the subspace, along with the steady-state behavior of the adaptation gate, suggested that adjustments were necessary to restore the proper functioning of the RyRs. To optimize the performance of the model, the minimum and maximum values were increased. These changes aimed to enhance the gate's responsiveness, ensuring that the opening and closing gates of the RyRs

could operate within their intended range.

Additionally, based on the steady-state analysis, a shift of 0.1 was applied in the steady-state equation of the adaptation gate. This was crucial in recalibrating the gate's behavior according to the calcium dynamics.

Consequently, after setting the proper value the ability of model in representing the ischemia-induced hyperkalemia improved (Figure 5).

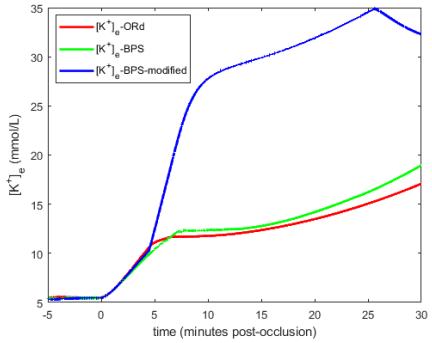

Figure 5. The improved visualization of ischemia-induced hyperkalemia by BPS model.

4. Conclusion and Future Development

The main conclusion of this study is that the BPS model, with its original structure, fails to correctly simulate the physiological effects of the progressive acute ischemia. This failure is primarily due to the inadequate performance of the opening and closing gates of the RyR receptor. By modifying a third parameter, the adaptation gate, which influences the functioning of the other two gates, we were able to improve the performance of the BPS model.

The key point to be focused on for improving the performance of the model could be following other strategies for tuning the performance of RyRs according to the calcium level.

Acknowledgments

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