Computational Analysis of Vulnerability to Reentry in Acute Myocardial Ischemia

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Abstract

The influence of each ischemic component (hypoxia, hyperkalemia, and acidosis) on arrhythmogenesis is controversial and difficult to study experimentally. In the present study, we investigate how the different ischemic components affect the vulnerable window (VW) for reentry using computational simulations.

Simulations were performed in a 3D biventricular model that includes a realistic ischemic region and the His-Purkinje conduction system. At the cellular level, we used a modified version of the O'Hara action potential model adapted to simulate acute ischemia. Three different levels of ischemia were simulated: mild, moderate, and severe. The effects on the width of the VW of each ischemic parameter were analyzed.

The model allowed us to obtain a realistic reentrant pattern corresponding to ventricular tachycardia in all simulations. Results suggest that the ischemic level plays an important role in the generation of reentries. Furthermore, hypoxia has the most significant effect on the width of the VW. The presence of Purkinje system is key to the generation of reentries.

1. Introduction

Myocardial ischemia is a cardiac disease caused by the block of blood flow to the heart muscle. As a result, a set of electrophysiological alterations occurs in the tissue that increase the likelihood of ventricular arrhythmias [1].

It is well known that hyperkalemia, hypoxia and acidosis are the main components of acute ischemia that induce these alterations. However, the influence of each ischemic component on arrhythmogenesis is controversial and difficult to study experimentally. Thus, computational simulations have served as a complementary tool to understand the mechanisms that induce arrhythmias. Indeed, several studies have analyzed the separate or combined effects of the ischemic components in the reentry initiation [2], [3], although none in a 3D human model that includes a realistic ischemic region and the His-Purkinje system. The role that this last element plays during an arrhythmic event is still not completely understand and it is also an important research topic.

The aim of this study is to investigate how the different ischemic components affect the vulnerable window (VW) for reentry using computational simulations.

2. Methods

The 3D biventricular model including the realistic geometry of the ischemic region was a model previously development by our group [4]. It was built from DE-MRI images of a patient suffering from myocardial infarction. Myocardium anisotropy was introduced via fiber orientation, while transmural heterogeneity was assigned in the model by defining the different zones: endocardium, mid-myocardium, and epicardium. The geometry of the ischemic central zone (ICZ) and border zone (BZ) was obtained based on the gray intensity of each pixel [4] (Figure 1).

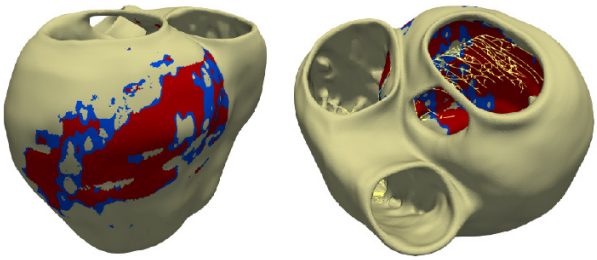

Figure 1. Model of the human ventricles showing the ischemic central zone (red), border zone (blue) and normal zone (khaki). Yellow traces represent the His-Purkinje system.

The His-Purkinje system (HPS) network used in this work was the same network developed in our previous study [5]. It comprises two and three main branches in its

right and left section, respectively. These branches are divided in several sub-branches, which are connected with the myocardium through the Purkinje-Muscle junctions.

Our simulations were performed using a modified version of the O'Hara ventricular action potential model [6], that includes the changes described in our previous work [5]. Alteration caused by acute ischemia was introduced in the model by modifying and incorporating several currents.

To simulate the changes in the intracellular ATP and ADP ($[ATP]_i$ and $[ADP]_i$, respectively) due to hypoxia, we added the ATP-sensitive K^+ current ($I_{K(ATP)}$) proposed by Ferrero et al. [7] and we adjusted it to human myocites by changing the maximum conductance and the sensitivity to $[ATP]_i$ and $[ADP]_i$ based on data from Babenko et al. [8]. Furthermore, different scaling factors that depend on $[ATP]_i$ and $[ADP]_i$ were introduced in the formulations of the Na^+/K^+, sarcolemmal Ca^{2+} and SERCA pumps, as in Cortassa et al. [9]. Acidosis was incorporated in the model reformulating the activation and inactivation gates of the L-type Ca^{2+} current (I_{CaL}) and adding a scaling factor in the equation of the I_{CaL} to mimic the experiments by Saegusa et al. [10]. Also, the fast and late Na^+ currents (I_{Na} and I_{NaL}, respectively) and the Na^+/K^+ pump were multiplied by different scaling factors that depend on extracellular and intracellular pH (pH_o and pH_i, respectively), and LPC. Finally, to simulate the hyperkalemia effect, we simply raised the extracellular potassium concentration ($[K^+]_o$).

Ischemic parameter values for the ICZ were adjusted to simulate three different severities of acute ischemia: mild, moderate, and severe. These severities correspond to minutes 2.5, 5 and 10 of acute ischemia, respectively (Table 1). For the BZ, each ischemic parameter was lineally varied from its normal value to its ischemic value. The transition of $[K^+]_o$, pH_i, pH_o and LPC occurred along the entire width of the BZ, while $[ATP]_i$ and $[ADP]_i$ gradients occurred in the proximal 10% of the BZ.

Table 1. Parameter values of the cell model in the ICZ for mild, moderate and severe ischemic conditions.

Parameter	Healthy	Mild	Moderate	Severe
$[K^+]_o$ (mM)	5.4	8.0	10.0	12.0
$[ATP]_i$ (mM)	10.0	8.5	7.0	4.0
$[ADP]_i$ (μM)	15.0	36.3	57.5	100.0
pHi	7.2	7.05	6.9	6.6
pHo	7.4	7.25	7.1	6.8
LPC (μM)	2.0	2.8	3.5	5.0

The AP model used for Purkinje fibers was developed by Stewart et al. [11]. However, due to the lack of experimental data during acute ischemia, hyperkalemia was the only effect introduced in the model by increasing $[K^+]_o$ as in the nearest cardiomyocyte.

To mimic the sinus rhythm, His bundle was paced at a BCL of 600ms (S1). To mimic the ectopic beat [12], we applied a premature stimulus (S2) in the BZ after the fifth beat S1 at different coupling intervals (CI) (interval between S1 and S2). The vulnerable window (VW) was computed as the range of CIs that produced two or more reentrant cycles.

3. Results

3.1. Effects of acute ischemia in the action potential

Figure 2A shows the map of APD variation during a moderate ischemic condition. The ICZ is delineated with the black lines. During control simulations, the APD values in the myocardium ranged 233–347ms, with an APD maximal in the locations of PMJs and an APD minimal found in regions close to the latest activated area on the epicardium.

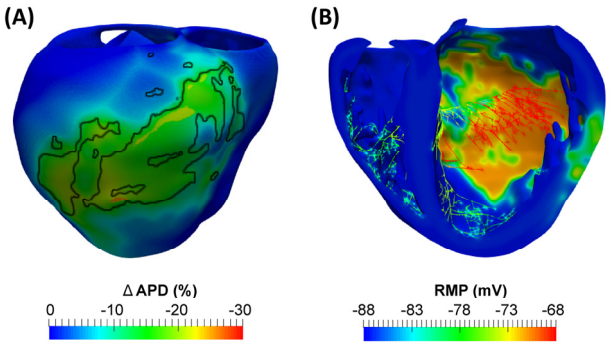

Figure 2. Maps of (A) APD variation (ΔAPD) and (B) resting membrane potential (RMP) during simulation of moderate ischemia. The black trace shows the ICZ.

Under moderate ischemia, the maximal APD was located at functional PMJs, while the minimal APD was found in the ICZ. The APD was reduced by 27% of its control value. This reduction was heterogeneous across the ischemic region as in experimental observations [13].

Figure 2B shows the resting membrane potential (RMP) under moderate ischemic conditions. In normoxic conditions, the RMP was approximately -88mV. In pathological conditions, RMP increases to less negative values. Simulation results show a RMP of -68 mV in the ICZ under a moderate ischemia, while in the BZ, the RMP varies between its normal and ischemic value.

3.2. Effect of ischemia in the generation of reentries

To assess the influence of each ischemic component on the onset of reentries, the vulnerable window (VW) for reentry was computed during different severities of acute ischemia (Figure 3).

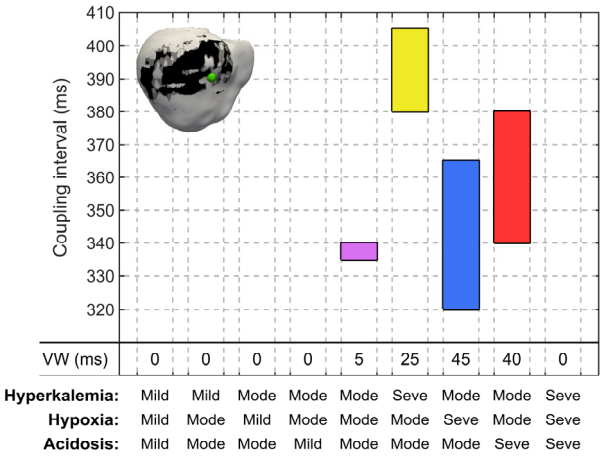

Figure 3. Vulnerable window (VW) for different severities of acute ischemia, using the model that include the CCS. Stimulation point is showed in light green inside the inset.

Simulations results show a VW of ≈ 5ms under moderate ischemia in all ischemic components, with a range of arrhythmic CIs between 335 and 340ms (magenta). An individual increment of hyperkalemia (yellow), hypoxia (blue) and acidosis (red) from moderate to severe led to widening of the VW to 25ms (CIs between 380 and 405ms), 45ms (CIs between 320 and 365ms) and 40ms (CIs between 340 and 380ms), respectively. However, no reentries were generated when all ischemic components were changed to severe conditions (VW = 0ms). Thus, our model suggests that an individual and combined increment could produce different effects in the width of the VW. On the other hand, a reduction alone or in conjunction of the three ischemic components from a moderate to mild condition did not trigger reentries in all cases.

Figure 5 shows an example of reentry using the anatomical model in which a premature stimuls is delivered within the VW. A figure-of-eight reentry was obtained during the simulation Indeed, a wavefront generated by the premature stimulus (S2) in the BZ led to two circus movement around the ICZ. These movements were completed at 350ms after S2 application.

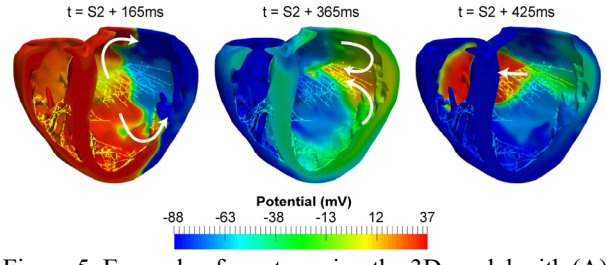

Figure 5. Example of reentry using the 3D model with (A) and without (B) cardiac conduction system. Premature stimulus (S2) was applied 365ms after fifth sinus beat.

4. Discussion

In this work, we investigated the effects of each component of ischemia in the generation of reentries. Our detailed AP model together with a realistic anatomical model, allowed us to obtain a reentrant pattern corresponding to ventricular tachycardia in all simulations. Furthermore, electrical alterations in the ischemic tissue, such as an increment in the RMP, a reduction of the conduction velocity and APD shortening were seen in our simulations, in concordance with Dutta *et al.* [14].

The ischemic severity played an important role in the generation of reentries. Indeed, our results show that reentries could be limited to an intermediate condition of acute ischemia (around 5 minutes of ischemia), as in the experimental study by Kaplinsky *et al.* in [15]. In this last study, the authors reported a peak of arrhythmic events between 5 and 6 minutes after artery occlusion. On the other hand, our simulation results also show that a change in the hyperkalemia, hypoxia and acidosis severity affects the VW, although in different degrees. Hypoxia was the ischemic component with the most significant effect on the width of the VW. This result agrees with Ferrero et al. [16], who suggested that hypoxia could be the most pro-arrhythmic component of ischemia. In addition, Lawson et al. [17] reported that the most critical factor in the onset of reentry is the wavelength (product between APD and CV), with hypoxia the primary determinant of this factor.

5. Conclusion

In this work, simulation results showed that the ischemic severity plays an important role in the generation of reentries. Furthermore, hypoxia has the most significant effect on the width of the VW.

Acknowledgments

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