







Understanding Ventricular Tachyarrhythmias Related to Acute Myocardial Ischemia: A Computational Modeling Approach

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Abstract. This paper describes a computational approach designed to study ventricular tachyarrhythmias arising from acute myocardial ischemia. Since these cardiac disorders can frequently lead to sudden cardiac death, understanding their mechanisms is key to improving their diagnosis and therapy. The use of computational simulations based on multiscale mathematical modeling has proved to be a powerful tool in unraveling the causes of this phenomenon. In the first part of this work, we reformulated a model of the ischemic human ventricular cell to simulate the features of the action potentials during acute ischemia. We then incorporated the model into an electrophysiologically-detailed three-dimensional virtual human heart, which was able to reproduce the typical ventricular tachyarrhythmias in the first 15 min of ischemia with rhythms resembling ventricular fibrillation. The results suggest that the extracellular potassium concentration and the presence of a wash-out subendocardial zone are key factors in the vulnerability of the ischemic myocardium to arrhythmias.

Keywords: Computational modeling · Myocardial ischemia · Ventricular tachyarrhythmias · Action potential · Hyperkalemia

1 Introduction

Acute myocardial ischemia is one of the leading causes of mortality all over the world [1]. Indeed, sudden cardiac death is a frequent consequence of acute myocardial ischemia in the first 10 to 15 min after the onset of coronary artery occlusion. The reason is the appearance of potentially mortal ventricular tachyarrhythmias such as ventricular fibrillation (VF) [2]. The ischemia-related development of hypoxia (i.e. lack of oxygen), hyperkalemia (i.e. accumulation of potassium in the extracellular medium) and acidosis (i.e. reduced pH) alters the characteristics

of the cellular action potentials (AP) and the myocardial substrate, increasing the likelihood of the appearance of reentrant arrhythmias such as VF [3].

Since the acute phase of myocardial ischemia is a highly unstable situation (both from the metabolic and electrophysiological point of view), it is very difficult (or even impossible) to completely understand the mechanisms that lead to the appearance of reentry by purely experimental means. For instance, the direct influence of hypoxia, hyperkalemia and acidosis on the likelihood of suffering an arrhythmia cannot be determined experimentally. However, computational simulations have proven to be a powerful aid in understanding the intricate mechanisms of ischemia-induced arrhythmias [4]. Since the first mathematical models of the acutely ischemic cardiac cell were developed [5–7], they have been used to throw light in the electrophysiologic basis and consequences of the pathology [4].

The aim of this work was therefore to (a) reformulate a cellular model of acute ischemia and adapt it to human cardiac cells, and (b) study the mechanisms of VF in a three-dimensional model of human cardiac ventricles, including the relevant myocardial anatomical and structural features (i.e. fiber orientation and central and border ischemic zones).

2 Materials and Methods

2.1 Background of the Computational Modeling Approach

Considerable efforts have been made in the last twenty-five years to adapt AP models to simulate acute ischemia (see [4] for review). Previous approaches have focused on reformulating and/or adapting existing AP models of different animal species (e.g. guinea pig, rabbit and dog) to account for ischemic features, mainly the effects of hypoxia on the ATP-sensitive K^+ current ($I_{K(ATP)}$) [5–7], the causes of hyperkalemia [8], and the effects of acidosis [7, 9, 10]. These models have then been used to study the effects of ischemia in realistic virtual 3D models of the heart [9–11]. However, although these models were based on human non-ischemic current data, the formulation of important ischemic-related currents, such as the $I_{K(ATP)}$, were based on data from other animal species, and the effects of ATP, ADP and other ischemia-related metabolites on the ATP-dependent pumps were not included.

2.2 Single Ischemic Cell Model

In order to develop a more comprehensive ischemic model of the human ventricular cell, a modified version [12] of the O’Hara model of the ventricular human AP [13] was used as the basal model in the present study. Since the original model was not intended to simulate acute ischemia, we incorporated new currents and reformulated others to account for the changes exerted by hypoxia, hyperkalemia and acidosis.

Hypoxia reduces intracellular ATP ($[ATP]_i$) and rises intracellular ADP ($[ADP]_i$). To introduce these changes into the model, we first did so in a model

of the ATP-sensitive K^+ current ($I_{K(ATP)}$) based on the formulation proposed by Ferrero et al. [5]. In order to adapt this model to human ventricular cells, we changed the maximum conductance and the sensitivity to $[ATP]_i$ and $[ADP]_i$, using experimental data from Babenko et al. [14]. Following the model proposed by Cortassa et al. [15], we also introduced different multiplication factors that depended on $[ATP]_i$ and $[ADP]_i$ in the formulations of the ATP-dependent pumps (i.e. the Na^+/K^+ , sarcolemmal Ca^+ and SERCA pumps). The values of the parameters related to the ATP and ADP effects are shown in Table 1. In order to account for acidosis, we introduced multiplying factors that depend on intracellular and extracellular pH and LPC into the fast and late Na^+ currents, the L-type Ca^+ current and the Na^+/K^+ pump. Finally, to account for hyperkalemia, we raised the extracellular potassium concentration ($[K^+]_o$) to typical acutely ischemic levels.

Table 1. Ischemia-related parameters in the model compared to the previous model [10]. Data for $I_{K(ATP)}$ corresponds to $[ADP]_i = 0$. Last column shows source of the model parameters.

Ionic current	Parameter	Ref. [10]	Our model	Data from
$I_{K(ATP)}$	$K_{m,ATP}$	0.035 mM	0.017 mM	[14]
	H	1.5	0.9	[14]
I_{NaK}	K_{ATP}	Absent	0.163 mM	[15]
	K_{ADP}	Absent	0.002 mM	[15]
SERCA	K_{ATP}	Absent	5.100 mM	[15]
	K_{ADP}	Absent	0.140 mM	[15]
I_{pCa}	K_{ATP}	Absent	0.230 mM	[15]
	K_{ADP}	Absent	1.000 mM	[15]

The stimulation protocol consisted of delivering a train of pulses 1 millisecond in duration with an amplitude 50% above diastolic threshold. The cell was paced at a basic cycle length (BCL) of 800 ms, which corresponds to a cardiac frequency of 75 beats per minute, for 10 min in order to achieve a steady-state. The APs shown in Fig. 2 and the values of action potential duration at 90% repolarization (APD_{90}) are those of the last AP of the series. The model was solved using Matlab(R) software.

2.3 Three-Dimensional Heart Model

The anatomically-based model of the human heart was similar to a model previously developed by our group [10]. Based on DT-MRI images, it accurately represents the geometry of both ventricles of a healthy human subject, including realistic fiber orientation. It also includes transmural electrophysiologic heterogeneity, which was introduced into the model by defining three distinct zones

(endocardium, midmyocardium and epicardium), as described in [10], in each of which the appropriate version of the O'Hara model was used.

To simulate acute regional ischemia, a central ischemic zone (CZ) was defined to mimic the proximal occlusion of the left anterior descending coronary artery (LAD). Surrounding the CZ, ischemic border zones (BZ) of different widths were defined as described in [7, 10]. The BZ for $[ATP]_i$ and $[ADP]_i$ had a width of 1 mm [16], while the width of the BZ for pH, LPC and $[K^+]_o$ was 1 cm [16]. Gradients of the relevant ischemic-related parameters were introduced into each BZ as proposed in [16] (see Fig. 1(A)). A wash-out zone was included in some simulations, consisting of a normal (i.e. non-ischemic) zone in the subendocardium $100\ \mu\text{m}$ in width [17].

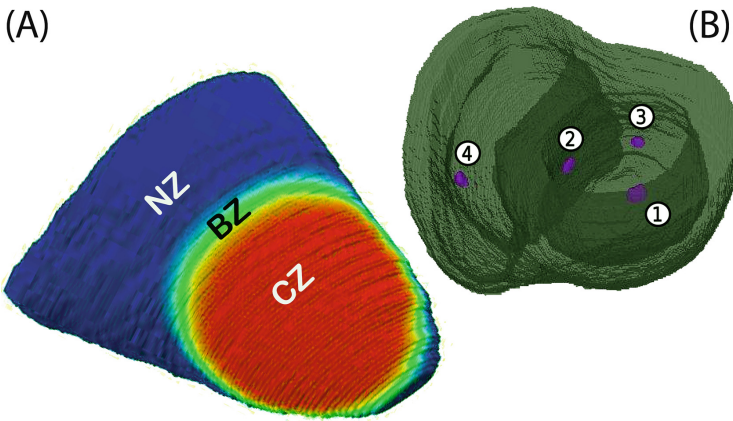


Fig. 1. (A) Three-dimensional human bi-ventricular model seen from the right epicardium. CZ: central ischemic zone; BZ: ischemic border zone; NZ: normal zone. Color indicates gradients of the ischemic-related parameters in each zone. (B) Sites of pacing for normal sinus activation.

The heart was paced for 1 min in four selected locations in the subendocardium (see Fig. 1(B)) to mimic sinus activation, and an extra-stimulus was delivered at different locations within the BZ to simulate the initiation of an ectopic beat [2]. The extra-stimulus was delivered at different coupling intervals (CI) (i.e. time after the onset of the last sinus beat), and the vulnerable window (VW) for reentry was defined as the range of CIs within which an extra-stimulus elicits reentrant activity (as in [7]). The model was solved by using the Finite Element Method as described in [10].

3 Results and Discussion

3.1 Effects of Ischemia at the Cellular Level

Figure 2 shows APs corresponding to control (i.e. normoxic) conditions (blue thin curve) and acutely ischemic conditions (red thick curve). In the control

simulation, the values chosen for the ischemia-related parameters were $[\text{ATP}]_i = 7$ mmol/L, $[\text{ADP}]_i = 15 \mu\text{mol/L}$, $\text{pH}_i = 7.2$, $\text{pH}_o = 7.4$, $[\text{LPC}]_i = 2 \mu\text{mol/L}$, and $[\text{K}^+]_o = 5.4$ mmol/L. In the ischemic case, values corresponded to 15 min of ischemia ($[\text{ATP}]_i = 2.3$ mmol/L, $[\text{ADP}]_i = 140 \mu\text{mol/L}$, $\text{pH}_i = 6.2$, $\text{pH}_o = 6.4$, $[\text{LPC}]_i = 5 \mu\text{mol/L}$, and $[\text{K}^+]_o = 10$ mmol/L). The values of APD_{90} were 270 ms and 135 ms, respectively.

The AP waveforms shown in the figure closely resemble the waveforms of experimentally measured APs in control and ischemic conditions [18]. The upstroke of the ischemic AP is divided into two phases, with the first one carried by sodium current through the ischemic-depressed fast Na^+ current, whilst the second one is sustained by calcium current flowing through the L-type Ca^{2+} current. The values of APD_{90} are in accordance with those measured in human normoxic and ischemic APs [19].

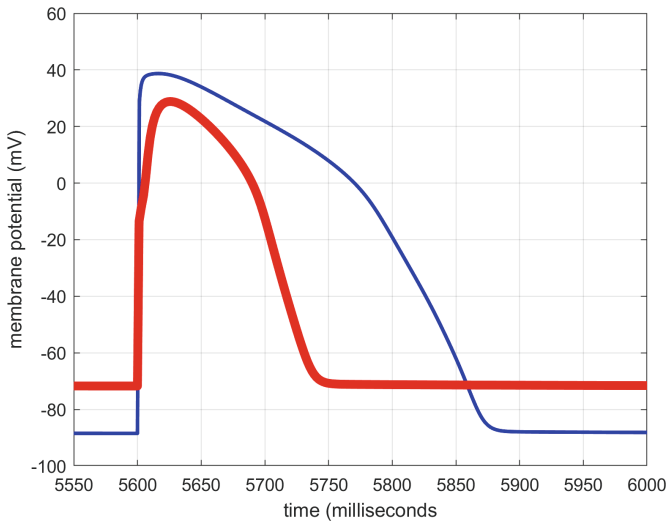


Fig. 2. Action potentials under control conditions (blue thin curve) and 15-min of myocardial ischemia (red thick curve). See text for details.

3.2 Reentrant Arrhythmias in a 3D Model of the Human Ventricles

We then incorporated the cellular ischemic model into the 3D heart model described in the Methods section and carried out simulations as described therein. Reentrant activity was elicited when we introduced an extra-stimulus within a certain range of CIs. Figure 3 shows an example of such reentry. At 2688 millisecond, an activation wavefront initiated by the extra-stimulus travels counterclockwise around and partially invades the CZ. This wavefront completes a 270° rotation at 2760 ms and 2832 ms and gives rise to a rotor-like reentry (2904 ms), which is typical in acute myocardial ischemic arrhythmias [18].

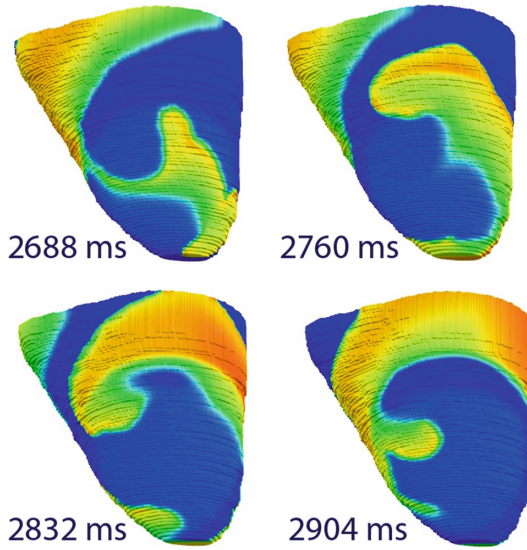


Fig. 3. Example of simulated reentrant activity in the acutely ischemic heart. See text for details

Table 2. Beginning (CI_{ini}) and ending (CI_{fin}) of the vulnerable window, and value (VW) of the vulnerable window, for different simulation conditions.

Wash-out zone	$[K^+]_o$ (mM)	CI_{ini} (ms)	CI_{fin} (ms)	VW (ms)
Yes	7.5	250	270	20
	8.5	265	280	15
	9.5	–	–	0
No	7.5–9.5	–	–	0

Once it was clear that the model was able to reproduce typical ischemia-related reentrant activity, we used it to quantify the VW duration under different conditions. The results are shown in Table 2. When the wash-out zone was included in the model, the duration of the VW for sustained reentry was approximately 20 ms for a value of $[K^+]_o = 7$ mmol/L. When more severe hyperkalemia was simulated ($[K^+]_o = 8$ mmol/L), the size of the VW decreased to 15 ms, indicating that the myocardium was less vulnerable to arrhythmias in this case. No reentrant activity was found for $[K^+]_o = 9$ mmol/L.

Finally, the effect of the presence of the subendocardial wash-out zone was assessed. When this was removed from the model it was impossible to obtain reentrant activity in the simulations for $[K^+]_o = 7$ mmol/L, $[K^+]_o = 8$ mmol/L or $[K^+]_o = 9$ mmol/L, indicating that the wash-out zone has a protective effect

during acute myocardial ischemia. These results agree with those in [10], while the differences are due to the fact that the present model was based on human $I_{K(ATP)}$ current data and the effects of ATP and ADP on the ATP-dependent pumps were included.

4 Conclusions

The results obtained indicate that an anatomically-based 3D model of the acutely-ischemic human ventricles is able to reproduce the reentrant activity typically found in experimental and clinical observations that can lead to sudden cardiac death. The model shows that the degree of hyperkalemia is a key factor in determining the vulnerability of the myocardium to arrhythmias, with moderate hyperkalemia ($[K^+]_o = 7 \text{ mmol/L}$) being the worst scenario, while the presence of the subendocardial wash-out normoxic zone protects the myocardium against arrhythmias.

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