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Vulnerability in regionally ischemic human heart. Effect of the extracellular potassium concentration

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ABSTRACT

Ventricular tachycardia and ventricular fibrillation are two types of cardiac arrhythmias that usually occur during acute ischemia and frequently lead to sudden death. Pro-arrhythmic mechanisms related to acute ischemia have been extensively investigated, although often in animal models rather than in human. In this work, we investigate how hyperkalemia affects the vulnerable window to reentry and the reentry patterns in the heterogeneous substrate caused by acute regional ischemia using an anatomically and biophysically detailed human biventricular model. The ischemic region was located in the inferolateral and posterior side of the left ventricle, mimicking the occlusion of the circumflex artery, and includes a wash-out zone not affected by ischemia located in the endocardium. Realistic heterogeneity and fiber anisotropy have been considered in the model. An electrophysiologically detailed human action potential model has been modified to simulate ischemic conditions. The model predicts the generation of sustained reentrant activity in the form of single and double circuits around an area of block within the ischemic zone for K^+ concentrations below 9 mM, with the reentrant activity corresponding to ventricular tachycardia in all cases. Our results also suggest that the wash-out zone is a potential pro-arrhythmic factor that favors sustained ventricular tachycardia.

1. Introduction

Ventricular tachycardia and fibrillation are known to be two types of cardiac arrhythmias that usually take place during acute ischemia, and frequently lead to sudden death [27]. Even though these arrhythmias arise from different conditions, ischemia is the most important perpetrator among them. The interruption of blood irrigation to the myocardium during acute ischemia has two main consequences from an electrophysiological point of view. Together with the reduction in nutrient delivery, the myocardium suffers a reduction in oxygen supply (hypoxia), an increase of extracellular potassium concentration $[K^+]_o$ (hyperkalemia), and an acidification of the underlying tissue (acidosis). These metabolic changes within the injured region cause significant alterations in the action potential (AP), a reduction in excitability and conduction velocity (CV), and an increase in the effective refractive period (ERP) among others [1,17]. In addition, these changes do not occur homogeneously within the injured region. In general, the impact of ischemia in the myocardium is characterised by a high degree of heterogeneity, both intramurally and transmurally, providing an important pro-arrhythmic substrate [3,15].

Pro-arrhythmic mechanisms of acute ischemia have been extensively investigated, although often in animal models rather than in human. Seminal studies by Janse et al. [16,17] in porcine and canine hearts highlight the complexity of the pro-arrhythmic and spatio-temporally dynamic substrate in acute ischemia. They observed that heterogeneity in excitability and repolarization properties across the borderzone leads to the establishment of reentry around the ischemic region after premature excitation [17,34]. The same studies also showed intramural reentry in certain cases, highlighting the potential variability in the mechanisms. However, the mechanisms that determine reentry formation and intramural patterns in acute ischemia in the three-dimensional human heart remain unclear, due to the low resolution of intramural recordings. In this regard, computer simulations of arrhythmias in three dimensional virtual human hearts may overcome these limitations and help to better understand the mechanisms of reentry initiation

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and maintenance, as well as the interactions and synergies between the different scales.

In the past 20 years, mathematical modeling and computer simulations in electrophysiology have become a useful tool in analyzing myocardial arrhythmias [26]. In one of the first works on acute ischemia by Ferrero et al. [7], the authors analyze the role that metabolic changes produced during ischemia have on the electrophysiological behavior of cardiac tissue. However, these and subsequent simulations were limited to two dimensional tissue preparations [7,32], providing only a partial view of the problem. Three dimensional simulations have been limited to the globally ischemic heart [25], with limited work performed in modeling the human heart subjected to acute ischemic conditions [5,13,33]. In this regard, Weiss et al. [33], account for heterogeneities caused by ischemia, as well as AP duration (APD) differences, both transmurally and apex to base. However, their action potential under acute ischemic conditions used the model proposed by Ferrero et al. [6] for guinea pigs and did not report reentrant activity. Heidenreich et al. [13] developed a human acute ischemic heart accounting for realistic fiber orientation and transmural heterogeneities. Their model was able to predict the generation of non sustained reentry, which patterns were in partial agreement with those reported experimentally [15]. Dutta et al. [5] have investigated on how reduced repolarization increases arrhythmic risk in the heterogeneous substrate caused by acute myocardial ischemia. In their work, Dutta et al. [5] developed a human ventricular biophysically-detailed model with acute regional ischemia. Even tough macro-reentries around the ischemic zone were reported, these reentries self-terminated before completing three complete circuits, i.e., only non sustained reentry was achieved.

In this work, we investigate how hyperkalemia affects the vulnerable window to reentry and the reentry patterns in the heterogeneous substrate caused by acute regional ischemia, using an anatomically and biophysically detailed human biventricular model. This investigation develops on our previous model [13] based on the monodomain paradigm for simulating the propagation of APs in the heart. For the biophysical description of the AP under normal and ischemic conditions, the model proposed by ten Tusscher and Panfilov [30] (TP06) was used. In this regard, the model was modified to account for ischemia by incorporating an ATP sensitive Potassium, I_{KATP}, current. By analyzing high spatio-temporal resolution simulation data, we unravel the mechanisms associated with the observed reentrant patterns observed in acutely-ischemic ventricles.

2. Methods

Simulation of the ischemic heart requires both an accurate description of the organ comprising its muscular structure and heterogeneity, and an appropriate model of its electrophysiologic behavior. The following sections offer a detailed description of the anatomical and biophysical model of the heart used in the present investigation, as well as the numerical methods used in the computations.

2.1. Heart model

The anatomically-based multiscale model of the heart relies on a previous model developed by our group [13]. Briefly, the geometry and fiber orientations were obtained from diffusion tensor magnetic resonance images (DT-MRI) acquired at John Hopkins University [14]. A regular volumetric mesh was constructed from the segmented images with hexahedral elements with a resolution of 0.4 mm × 0.4 mm × 0.4 mm, resulting in 1.43 million nodes and 1.29 million hexahedral elements.

Transmural heterogeneity of the electrophysiological properties across the heart is necessary to accurately describe normal cardiac function. In this regard, transmural differences in the electrophysiological behavior of the cells were introduced in order to obtain an APD gradient from the endocardium to the epicardium, with the longest APD at the midendocardium [11]. This was achieved by defining a layered distribution that includes the three cell types defined in the TP06 models in a proportion of 43% of epicardial cells, 20% of endocardial cells, and the remaining 37% being occupied by midmyocardial cells according to the APD distribution reported in [11] for the healthy human heart. This distribution resulted in a positive T wave in all synthetic electrograms computed in the precordial leads as shown in Fig. 1, in addition to a normal progression of the QRS complex (for the case of acute ischemia under investigation). As in other works [5,13], the present model does not incorporate explicit apex-to-base APD heterogeneity.

2.2. Action potential model under ischemic conditions

All simulations were performed with a modified version of the ten Tusscher and Panfilov (TP06) model of the human AP [30]. The model describes with high degree of electrophysiological detail the principal transmembrane ionic currents: sodium current I_{Na}, L-type calcium current I_{CaL}, inward rectifying current I_{K1}, fast delayed rectifying current I_{Kr}, slow delayed rectifying current I_{Ks}, transient outward current I_{to}, sodium–calcium exchanger current I_{NaCa}, sodium–potassium pump current I_{NaK}, plateau calcium and potassium currents I_{pCa} and I_{pK} respectively, and background sodium and calcium currents I_{bNa} and I_{bCa}. In order to describe the electrophysiological changes caused by ischemia, the model was provided with a modified formulation of the ATP-sensitive K^+ current (I_{KATP}) proposed by Ferrero et al. [6]. The methodology was explained in detail in our previous work [13]. Briefly, the I_{KATP} current was formulated as

$$I_{KATP} = g_0 \left(\frac{[K_o^+]}{5.4} \right)^{0.24} f_M f_N f_T f_{ATP} (V - E_K), \tag{1}$$

where g_0 is the maximum channel conductance in the absence of Na^+, Mg^{2+} and ATP; f_M, f_N, f_T are inward-rectification-related factors given in [6] that we kept unaltered in the modified model; f_{ATP} is the fraction of open channels; V is the transmembrane potential; and E_K is the reversal potential of the channel (Nernst potential). The fraction of open channels, f_{ATP}, is given by [13]

$$f_{ATP} = \frac{1}{1 + ([ATP]_i / K_m)^H}, \tag{2}$$

where $[ATP]_i$ is the ATP intracellular concentration in mmol/L, with K_m (in mmol/L) and H (–) given by

$$K_m = \alpha (35.8 + 17.9 [ADP]_i^{0.256}, \tag{3}$$

$$H = 1.3 + 4.44 \exp(-0.09 [ADP]_i), \tag{4}$$

where $[ADP]_i$ is the intracellular concentration of ADP in μmol/L, and α a parameter that accounts for cellular heterogeneity. Parameter α was identified by fitting experimental data available for different animal models and cell types (see Fig. 2.2 in [13]) in addition to human data reported in Koumi et al. [20]. This approach has been adopted by others when developing an heterogeneous model of I_{KATP} [10,22]. Due to the absence of experimental data, our model of the ATP influence in the fraction of open channels in midmyocardial cells assumes a value of α that yields the same percentage reduction in APD as in endocardial cells. This decision was taken based on the results from Wilensky et al. [34] who found a 40% reduction in APD for cells 1 mm deep from the endocardial surface in the case of phase 1a ischemia (10 min after coronary occlusion).