

The Role of Purkinje Automaticity as an Arrhythmia Mechanism in Hyperkalaemia

Violeta Monasterio¹, Jesús Carro^{1,2}, Esther Pueyo^{2,3}, José F Rodríguez^{2,4}

¹ Universidad San Jorge, Villanueva de Gállego, Spain

² Universidad de Zaragoza, Zaragoza, Spain

³ CIBER-BBN, Zaragoza, Spain

⁴ Politecnico di Milano, Milano, Italy

Abstract

The pacemaker activity of Purkinje (PK) cells is usually suppressed by the sino-atrial (SA) node. Under abnormal conditions, PK cells may produce ectopic focal activity leading to tachycardia and fibrillation. This computational modelling work illustrates the potential role of PK automaticity as an arrhythmia mechanism in hyperkalaemia.

First, we investigated the automaticity of isolated PK cells under hyperkalaemic conditions. Second, the potential consequences of altered PK automaticity were explored in a 1-D model of a terminal PK fibre running through a hyperkalaemic zone. Hyperkalaemia was found to accelerate the autorhythmic period of isolated PK cells with respect to control. For extracellular potassium levels ≥ 7.2 mM, spontaneous action potentials (APs) appeared in the PK fibre, leading to conduction disturbances and complex combinations of spontaneous and stimulation-driven APs.

1. Introduction

Under normal conditions, the SA node is the prevailing pacemaker of the heart. Abnormal automaticity occurs when other cells, like cells in the atrio-ventricular node or in the His-Purkinje conduction system, undertake the SA node function [1]. Under pathological conditions, the SA node cells may reduce their rate of spontaneous depolarization. Even in the case of normal SA node functioning, some cells can develop rates of firing faster than that of the SA node. In particular, both reentrant-triggered and enhanced automatic rhythms can arise from the Purkinje (PK) fibre network, leading to ventricular arrhythmias [2].

In this work we study the influence of hyperkalaemia (that is, an increase in the extracellular potassium concentration $[K^+]_o$) in PK cells activity. Hyperkalaemia is one of the main physiological changes that occur in cardiac cells during acute ischaemia [3], and has been confirmed to

be an important factor in the genesis of reentrant-triggered rhythms at the PK-myocardium interface, since it regulates the range of intercellular coupling in which unidirectional conduction blocks may be induced [4].

In the present work we investigate the potential role of PK automaticity as an additional arrhythmia mechanism. For our computational simulation study we use two human action potential (AP) models: the ten Tusscher and Panfilov 2006 (TT06) endocardial model [5] and the Stewart et al. 2009 (ST09) model [6]. We start by studying the alterations in isolated PK cells automaticity under hyperkalaemia, and then we investigate the effects that those alterations have on the genesis of abnormal rhythms in a 1-D model of a PK fibre running towards the centre of an acutely hyperkalaemic endocardial zone.

2. Methods

First, the automaticity of isolated PK cells under hyperkalaemic conditions was investigated. Second, the effects of PK automaticity under hyperkalaemic conditions were explored in a 1-D model of the PK-ventricle subsystem. All simulations were carried out using the software ELVIRA [7].

2.1. Isolated Purkinje cells

The system of differential equations that govern the cellular electrical behaviour according to the ST09 model [6] was solved by using forward Euler integration with a time step $\Delta t = 0.02$ ms. Transmembrane potential (V_m) and all the other state variables were computed at each time step.

Hyperkalaemic conditions were simulated by increasing $[K^+]_o$ from 5.4 to 12.5 mM with 0.1-mM steps. For each $[K^+]_o$, the model was run without stimulation for 150 s, and the average cycle length (CL) of spontaneous APs between $t = 50$ s and $t = 150$ s was measured.

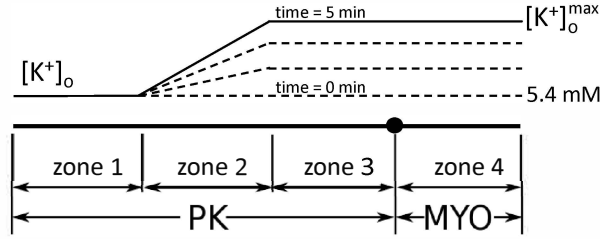


Figure 1. Purkinje-ventricle 1-D simulation setup.

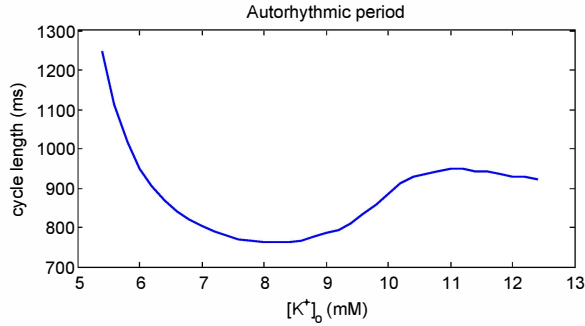


Figure 2. Average cycle length (CL) of spontaneous action potentials (APs) vs. $[K^+]_o$ in isolated PK cells.

2.2. 1-D Purkinje-ventricle tissue

The PK-ventricle subsystem was modelled as a 1-D tissue composed of 3 cm of PK cells (zones 1 to 3 in Figure 1) connected to 1 cm of endocardial cells (TT06, zone 4 in Figure 1). Electric propagation across the cardiac tissue was modelled with the monodomain model. Discretization was performed using a spatial interval of $\Delta x = 0.1$ mm and a time interval of $\Delta t = 0.02$ ms. Longitudinal conductivity was set to $\sigma_p = 0.0068$ mS/cm in zones 1 to 3 and to $\sigma_m = 0.0009$ mS/cm in zone 4, leading to conduction velocities of 2.1 m/s and 0.7 m/s respectively under control conditions, well within experimental ranges [8]. The Purkinje-myocardial junction was modelled as a resistor with $\sigma_p = 0.01$ mS/cm. The system of equations was solved using the software ELVIRA [7]. Twelve positions within the fibre were selected for further analysis in each simulation; those positions were located at $x_i - 0.5$, x_i , and $x_i + 0.5$ mm, with x_i being the central position in zone i .

The fibre was stimulated at the PK end, with current pulses of 1-ms duration and 1000-nA/pF amplitude, at CL = 1000 ms for 5 min. During that time, $[K^+]_o$ was uniformly increased from 5.4 mM to $[K^+]_o^{max}$ in zones 3 and 4, whereas $[K^+]_o$ remained at 5.4 mM in zone 1; in zone 2, $[K^+]_o$ varied linearly between the values in zones 1 and 3 (Figure 1). Simulations were carried out for $[K^+]_o^{max}$ of 5.4, 6.3, 7.2 and 8.1 mM.

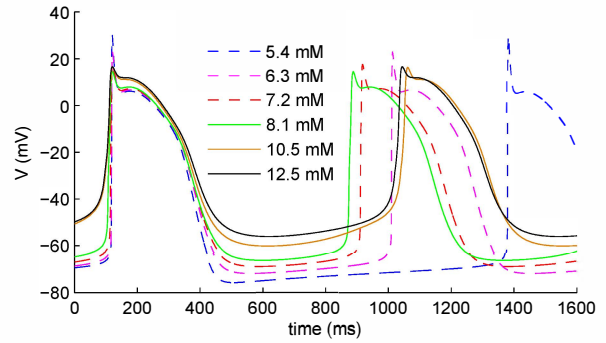


Figure 3. Spontaneous APs vs. $[K^+]_o$ in isolated PK cells. Traces were extracted from the last two seconds of each simulation and aligned for illustration purposes.

3. Results

3.1. Isolated Purkinje cells

The autorhythmic period of PK cells was strongly influenced by hyperkalaemia, with average CLs decreasing from 1248 ms ($[K^+]_o = 5.4$ mM) to a minimum of 762 ms ($[K^+]_o = 8.1$ mM) (Figure 2). AP-duration (APD) and resting potential (RP) were also affected by $[K^+]_o$. Figure 3 illustrates these results; APD increased from 310 ($[K^+]_o = 5.4$ mM) to 344 ($[K^+]_o = 12.5$ mM), and the most negative RP varied from -75.72 mV ($[K^+]_o = 5.4$ mM) to -56.02 ($[K^+]_o = 12.5$ mM).

3.2. 1-D Purkinje-ventricle tissue

In the PK-ventricle model, no automaticity was observed in PK cells for $[K^+]_o^{max} = 5.4$ and 6.3 mM. In those cases, stimulation-generated APs propagated from the PK end of the fibre towards the myocardium end without disturbances. Figure 4(a) illustrates this situation. APs are generated at the PK end every 1000 ms. The positive time delays between successive zones and the blue-red-black order in the zoom traces clearly indicate normal propagation towards the myocardium.

For $[K^+]_o^{max} = 7.2$ and 8.1 mM, PK automaticity was observed in the hyperkalaemic portion of the fibre (zone 3), which led to complex patterns of spontaneous and stimulation-driven APs by the end of the 5-min simulation. The time-course of this phenomenon was similar in both cases. Spontaneous APs appeared in zone 3 at $t = 226$ s for $[K^+]_o^{max} = 7.2$ mM and at $t = 156$ s for $[K^+]_o^{max} = 8.1$ mM. A few seconds later, spontaneous APs started to propagate backwards (towards zone 2). By $t = 250$ s ($[K^+]_o^{max} = 7.2$ mM) and $t = 176$ s ($[K^+]_o^{max} = 8.1$ mM) spontaneous APs reached the PK end of the fibre, creating mixed patterns of spontaneous and stimulation-driven

APs. An example is shown in Figure 4(b), where spontaneous APs have overridden stimulated APs due to their shorter CL. A little time after $t = 298.6$ ms, a spontaneous AP starts in zone 3 and propagates backwards (there is a positive time delay from zone 3 to zones 2 and 1, and within zones 2 and 1 the black–red–blue order of the traces indicate retrograde conduction), while a stimulation-driven AP is generated at the PK end at $t = 298.6$ ms and travels forward (towards the myocardium).

4. Discussion and conclusions

In this study we evaluated the effects of hyperkalaemia on PK automaticity. According to our results, mildly hyperkalaemic conditions may accelerate the rate of spontaneous discharge, while severe hyperkalaemic conditions seem to invert that tendency. This behaviour is consistent with some well-known effects of hyperkalaemia on cardiac cells [9]. An effect of mild hyperkalaemia is to shift the resting membrane potential to a less negative value. Although the threshold potential also becomes less negative, the magnitude of that change is smaller than the change in resting potential, so the net effect is to bring the resting potential closer to threshold potential, increasing cell excitability. On the other hand, the resting potential determines the number of voltage-gated sodium channels available for depolarization, which in turn determines the magnitude of the inward sodium current at the onset of phase 0 and thus the AP amplitude. As extracellular potassium levels increase, the resting membrane potential becomes less negative, reaching a point where the number of sodium channels available for depolarization severely decreases. The changes in threshold potential now are comparable to the changes in resting potential, so the cell becomes less excitable than in mild hyperkalaemia. These differences in excitability together with the progressive diastolic depolarization of PK cells may account for the differences in the autorhythmic period found in our study.

Our results on isolated PK cells showed changes in AP amplitude, RP and upstroke velocity that are consistent with the hypothesis above, and also with *in vitro* studies with human PK cells [10]. As a limitation, however, it should be noted that the changes found in APD are inconsistent with the literature [10, 11], since a shortening of APD has been reported under hyperkalaemia. To investigate whether the mechanisms behind this disagreement could also be affecting the automaticity rate, we performed a sensitivity analysis by varying the conductances and time constants of all currents in the ST09 model within $\pm 30\%$ of their default value, but we did not observe any direct relationship between changes in automaticity rate (mainly determined by I_f current) and the slight increase of APD. This observation, together with the fact that other human PK models also predict automaticity acceleration while

correctly reflecting APD shortening [12], suggest that it is unlikely that the two phenomena are coupled.

Hyperkalaemia has been found to potentiate conduction abnormalities in clinical studies, in which abnormal impulse formation has been observed as a result of acceleration of normal pacemakers or the emergence of ectopic pacemakers [13]. Unfortunately, experimental observations on the effects of hyperkalaemia on the automaticity of human PK cells are scarce and mostly anecdotal. Although results in this work can only be considered as preliminary, the abnormal rhythms and complex patterns found in the PK-ventricle simulations suggest that altered PK automaticity under hyperkalaemia may play an important role in the generation of ventricular arrhythmias.

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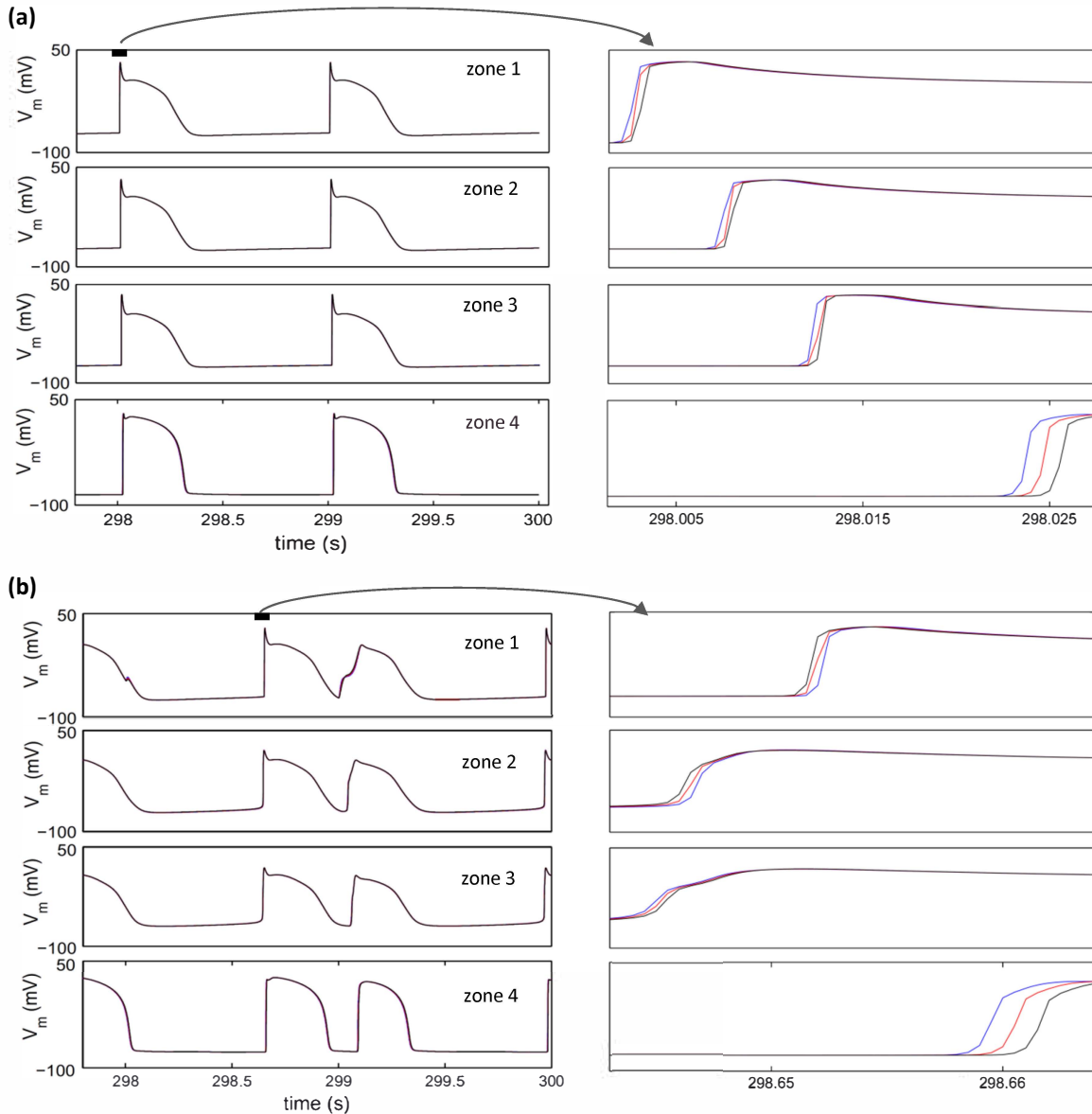


Figure 4. (a) 1-D simulation for $[K^+]_o^{max} = 5.4$ mM. Top to bottom panels represent zones 1 to 4 as defined in the text. The last two seconds of simulation are shown on the left; a zoom is shown on the right. Membrane potentials at positions $x_i - 0.5$, x_i , and $x_i + 0.5$ mm, with x_i being the central position in zone i , are shown in blue, red and black respectively. (b) Same representation for $[K^+]_o^{max} = 7.2$ mM results.

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Address for correspondence:

Violeta Monasterio (vmonasterio@usj.es)
 Universidad San Jorge
 50830 Villanueva de Gállego, Spain