Role of Extracellular Potassium and Cellular Uncoupling on the Electrical Activity of the Purkinje-Ventricle Subsystem: A Simulation Study

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Abstract

Arrhythmias induced by phase 1B of ischemia are poorly understood. A bidimensional computer model has been developed to study the interaction between a bundle of Purkinje fibers and a layer of ventricular ischemic tissue. The present work has focussed on the role of the increase of extracellular potassium concentration and changes in the cellular coupling provoked by 1B ischemia in ventricular tissue connected to Purkinje fibers. To simulate 1B ischemic conditions, we altered several electrophysiological parameters of the Luo-Rudy action potential model(Lrd00).

Our study suggests that a greater extracellular potassium concentration than 14.2 mmol/L and the moderate increase of cellular uncoupling induced by ischemia in a ventricular zone could cause conduction block in Purkinje to ventricle and conduction in ventricle to Purkinje, thus generating unidirectional block and reentry.

1. Introduction

Most of the deceases in the industrialized world caused by cardiac illnesses is due to cardiac sudden death, which in turn, in the greatest proportion is provoked by ischemia-induced ventricular fibrillation (VF). Experimental studies have shown that ventricular arrhythmias induced by ischemia in the first hour of the coronary occlusion are evident in two phases [1, 2]. The first phase (1A) occurs in canine hearts from 2 to 8 min of the onset of ischemia [3]. After a free arrhythmias period, a second phase (1B) is produced in the interval from 15 until 45 minutes of ischemia. Arrhythmias induced by phase 1B ischemia are poorly understood.

Several studies have shown a relationship between the uncoupling of the ventricular cells and the beginning of the phase 1B of arrhythmias. The incidence peak of ventricular arrhythmias is noticeable in the second increase of the resistance of the ventricular tissue induced by ischemia. The maximum increase registered in the resistance of the tissue has been from 50 to 175 % at 60 min of the onset of ischemia in many experimental species [3].

The Purkinje system has a fundamental role in ventricular activation. Purkinje-ventricle junctions (PVJs) are affected during an ischemic episode because the delay associated with PVJ is increased. In conditions of simulated ischemia an inhibition of conduction through the Purkinje-ventricle junctions has been observed [4]. One possible reason of this inhibition, could be the increase in the resistance of the gap junctions, which produces uncoupling between the Purkinje fibers and endocardium or subendocardium.

The goal of the present work was to study through computer simulations the role of the increase of extracellular potassium concentration and changes in the cellular coupling provoked by 1B ischemia in ventricular tissue connected to Purkinje fibers.

2. Methods

The interaction between Purkinje fibers and endocardial tissue under 1B ischemic conditions was modeled with the 2D model shown in figure 1. The model consists of a bundle of 10 Purkinje fibers connected by two Purkinje-ventricle junctions (PVJ1 and PVJ2) to a layer of ventricular ischemic tissue. The bundle of Purkinje fibers was formed by 5 $\times$ 452 nodes and the ventricular layer was compound of 175 $\times$ 150 nodes. Each node of Purkinje and ventricle had a square shape with dimensions dx = 100 μm and dy = 100 μm.

Ventricular tissue was divided in three zones: 1B central ischemic zone (CIZ1B), border zone (BZ) and normal zone (NZ). To simulate 1B conditions, several parameters in the Luo-Rudy ventricular model [5] were modified and have also been used in previous works [4, 6]. The parameters were adjusted according to a modified version developed by our group and based on Pollard and coworkers work [7]. In panel A of figure 1 are indicated the profiles for ventricular impedance (R_{endo}) and extracellular potassium concentration ($[K^+]_o$) that were modified in CIZ1B and BZ of ventricular tissue. The border zone had 10 mm

in length and inside this zone we considered 1 mm for hypoxia, 5 mm for acidosis and 10 mm for hyperkalemia.

The model was stimulated in the sites indicated in panel B of figure 1. The amplitude of the impulse was 1.2 times the diastolic threshold and had a duration of 2 ms.

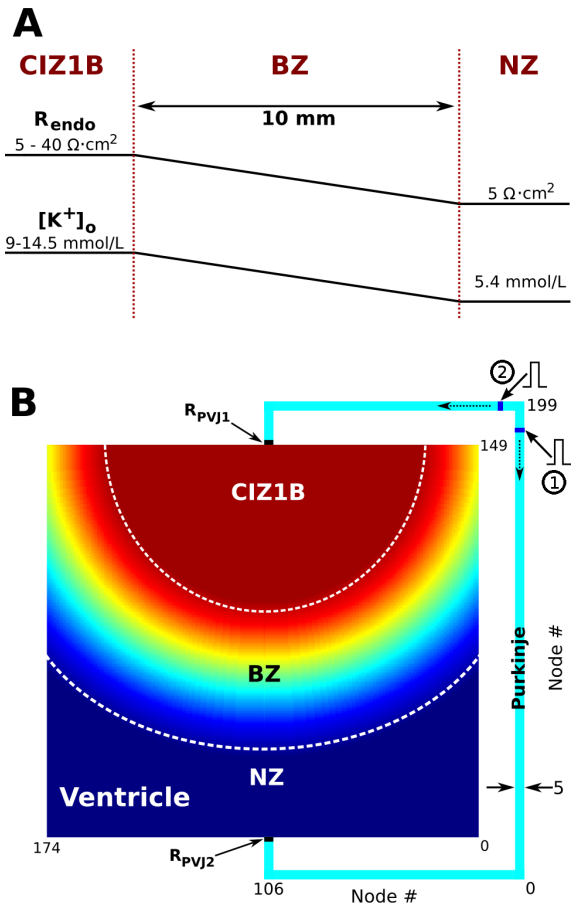

Figure 1. 2D model of a bundle of Purkinje fibers connected to a layer of endocardial tissue under 1B ischemic conditions.

3. Results

In a set of simulations, parameters to simulate 1B conditions were fixed in the model of figure 1. Extracellular potassium concentration was varied in a range of 5.4 to 14.5 mmol/L in the central ischemic zone. The increase of $[K^+]_o$ provoked two situations: a) Purkinje-ventricle conduction with reduction in the conduction velocity or b) unidirectional block (UDB) at the Purkinje-ventricle junction #1 (PVJ1). Figure 2 panel A shows 4 voltage snapshots at different simulation time. The model was stimulated in Purkinje at site 1 (see figure 1 panel B) and the wavefronts progressed to junctions PVJ1 and PVJ2 (t = 52 ms). One wavefront crossed PVJ1 continuing its propagation to CIZ1B zone of the ventricular tissue (t = 90 ms). The other wavefront crossed PVJ2 approaching the wavefront that got through PVJ1, both wavefronts collided near PVJ2 (t = 112 ms).

When $[K^+]_o$ was increased to 14.5 mmol/L, conduction block was observed in the ventricular cells of CIZ1B close to PVJ1. In panel B of figure 2 4 snapshots are shown for this case. Stimulus applied at site #1 of the model generated two wavefronts in the Purkinje fiber (t = 52 ms). The first wavefront crossed PVJ1 starting propagation in ventricular cells of the 1B central ischemic zone, but the wavefront extinguished (t = 90 ms). Second wavefront crossed PVJ2 propagating through the normal zone of the ventricular tissue (t = 112 ms). The second wavefront reached PVJ1 trying to continue the propagation through the Purkinje fiber (V-P conduction). As Purkinje cells were in refractoriness, the second wavefront could not restimulate the cells of the Purkinje fiber. APDs of CIZ1B cells were shorter, so these cells repolarized in first term, as shown in voltage snapshot 4 of panel B in figure 2.

The simulations showed that 1B conditions in ventricular tissue and particularly the increase of $[K^+]_o$ could provoke unidirectional block (UDB) in P-V conduction. The greater $[K^+]_o$ in ventricular CIZ1B, the greater probability of UDB.

A new set of simulations was conducted changing not only $[K^+]_o$ but also the coupling between Purkinje fiber and ventricular tissue. An increase of 100 % in the impedance of PVJ1 (R_{PVJ1} = 32 Ω·cm^2) caused conduction block from Purkinje to ventricle (P-V). In panel A of figure 3 4 snapshots are shown where other important 1B parameters were adjusted to the following values: R_{PVJ2} = 16 Ω·cm^2, R_{endo} = 5 Ω·cm^2 and $[K^+]_o$ = 11.5 mmol/L. In snapshot 1, an impulse was applied now at site 2 (see figure 1 panel B) of the 2D model generating two wavefronts (t = 52 ms). One wavefront was blocked just at PVJ1, the other crossed PVJ2 propagating through the ventricular normal zone (snapshots 2 and 3). Afterwards, the wavefront reached PVJ1 crossing the junction (V-P conduction) but Purkinje cells could not be reexcited (t = 178 ms). Unidirectional block was provoked by uncoupling Purkinje fiber and ventricular tissue. The greater uncoupling between Purkinje and ventricle, the greater probability of UDB.

The next set of simulations was used to study if coupling in ventricular cells affected the unidirectional block. When the resistance of the 1B central ischemic zone was increased in 60 % (R_{endo} = 8 Ω·cm^2), the conduction block was maintained. But, when the R_{endo} resistance was increased in 80 % (R_{endo} = 9 Ω·cm^2), the conduction block disappeared and conduction from Purkinje to ventricle was observed (see panel B in figure 3). With this value of ventricular impedance, wavefront collision occurred in cells

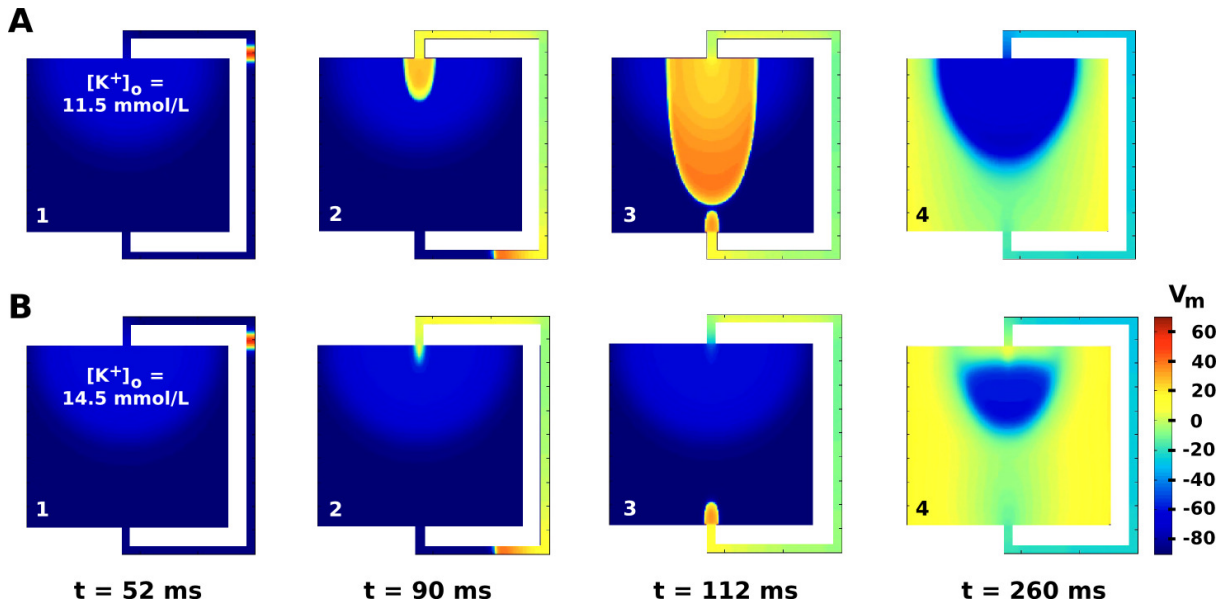

Figure 2. Voltage snapshots in the 2D model of a bundle of Purkinje fibers connected to a layer of endocardial tissue under 1B ischemic conditions at different time instants.

of Purkije fiber as indicated in snapshot 4 of panel B of figure 3. Also, when the R_{PVJ1} was fixed in a 50 % increase (R_{PVJ1} = 24 Ω·cm^2) and extracellular potassium concentration ($[K^+]_o$) was increased in a range from 9 to 14.5 mmol/L, unidirectional block was produced for $[K^+]_o$ greater than 14.2 mmol/L. The uncoupling of 1B ischemic tissue could improve P-V conduction.

4. Discussion

According to the results, 1B conditions in ventricular tissue may provoke unidirectional block in Purkinje-ventricle conduction close to PVJ. In a preparation of canine Purkinje fibers coupled to papillary muscle containing two Purkinje-muscle junctions (PMJs), Gilmour and coworkers also found that premature stimuli to Purkinje cells induced unidirectional anterograde conduction block at PMJ and retrograde conduction from papillary muscle across the same PMJ [8].

Uncoupling of Purkinje fiber and ventricular tissue produced unidirectional block close to Purkinje-ventricle junction #1. In a modeling study, Quan and Rudy determined that cellular uncoupling alone may produce unidirectional block. The model used consisted of one-dimensional ring of cardiac tissue [9]. Quan an Rudy did not use ischemia conditions in their simulations, they focused on cellular uncoupling and determined that the probability of unidirectional block induction was proportional to the degree of cellular uncoupling. Our results marked the importance of uncoupling, but we found that uncoupling between Purkinje and ventricle provoked a range where UDBs could occur. Further, moderate ventricular cellular uncoupling may facilitate unidirectional conduction block from Purkinje to ventricle.

An increase of 80 % in the coupling resistance between cells of CIZ1B of ventricular tissue produced the inhibition of unidirectional block in propagation from Purkinje fiber to ventricular tissue. Similarly, Morley and coworkers found a paradoxical propagation across Purkinje-ventricle junctions induced by reduced intercellular coupling [10]. They suggested that paradoxical propagation was produced by activation of quiescent PVJs increasing the number of PVJs where P-V conduction was successful. Our results are different, an active PVJ can change its state provoked by moderate uncoupling.

5. Conclusions

Our results show that a greater $[K^+]_o$ than 14.2 mmol/L and the moderate increase of cellular uncoupling induced by ischemia in a ventricular zone could cause conduction block in P-V and conduction in V-P, thus generating unidirectional block and reentry. This phenomenon could be related to the increased probability of arrhythmias arising during phase 1B of ischemia.

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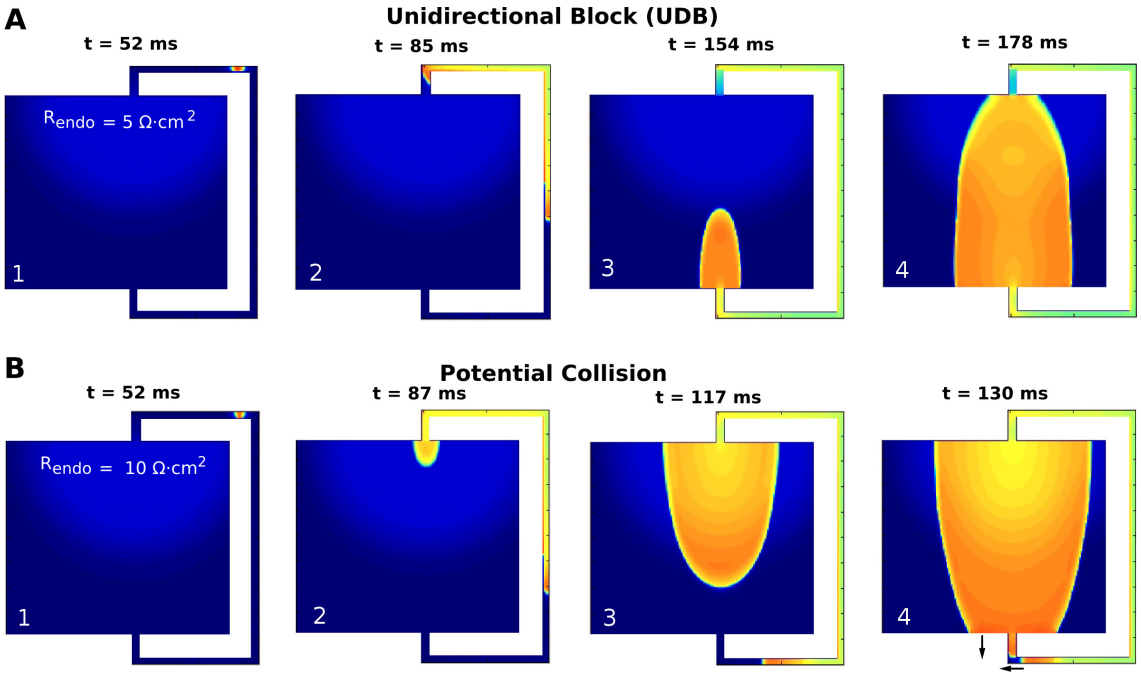

Figure 3. Voltage snapshots in the 2D model of a bundle of Purkinje fibers connected to a layer of endocardial tissue under 1B ischemic conditions at different time instants.

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