Safety in Purkinje to Ventricular Conduction and Reentrant Activity under Simulated 1B Ischemia

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Abstract

During the subacute phase of ischemia, electrophysiological alterations and cellular uncoupling set the stage for reentry. In the present work, we have developed a computational model of a fiber and a ring composed by Purkinje cells coupled to a ventricular fiber, which includes a 1B ischemic zone, a border zone and a normal zone. Simulations have been conducted to analyze the effects of cellular uncoupling and hyperkalemia on AP propagation.

The results have shown that propagation block (safety factor SF < 1) occurred for low and high ventricular coupling (R_{endo} 5 $\Omega \cdot cm^2$ and 40 $\Omega \cdot cm^2$ respectively) as long as hyperkalemia was severe. Additionally, intermediate cellular coupling favored propagation. In the ring model, reentry was obtained for low values of R_{endo}. In conclusion, cellular uncoupling during 1B ischemia and hyperkalemia are crucial factors in the generation of propagation block, and reentry.

1. Introduction

During myocardial ischemia, deep alterations in electrophysiological conditions arise and set the stage for malignant arrhythmias. Arrhythmogenic episodes have been experimentally and clinically observed during phase 1A of ischemia, i.e. within the first 10-15 minutes after coronary occlusion, but also during phase 1B, i.e. between 15 and 60 minutes after the onset of myocardial ischemia [1,2]. During this subacute phase, ischemic conditions are more severe and cellular uncoupling supposes an important factor in the generation of conduction blocks which can lead to reentrant activity.

To quantify the safeness in conduction, Shaw and Rudy formulated the Safety Factor (SF) calculation. They defined the safety factor for conduction as the ratio of charge generated by cell excitation to the minimal amount of charge required to produce the excitation [3]. A SF > 1 means that the amount of charge produced during excitation is greater than the charge required to provoke the excitation, i. e. successful conduction. If the SF < 1, the charge requirements are not satisfied, so the conduction is not successful [4]. Recently, Romero et al. simplified the SF calculation to evaluate conduction block in ischemic ventricular tissues [5] leading to reentry. In this way, it would be also of great interest the analysis of Purkinje to ventricular conduction (P-V conduction), as it is known to play a fundamental role in the process of cardiac excitation sequence.

It has been observed that Purkinje fibers are coupled to ventricular cardiac fibers at multiple sites, through Purkinje-ventricular junctions (PVJs). Conduction between Purkinje cells and ventricular fibers is discontinuous due to a conduction delay of approximately 3 to 6 ms. As ischemia alters the resistance of PVJs, uncoupling between Purkinje and ventricular regions arises [6]. This situation might provoke unidirectional block and slow conduction, conditions related to the generation of reentry. Additionally, uncoupling increases action potential duration (APD) of Purkinje cells setting the stage for triggered activity.

The aim of this study is to analyze the effects of cellular uncoupling in ventricular 1B ischemic tissue connected to Purkinje fibers on the generation of conduction blocks and reentry.

2. Methods

Computer simulations were performed using a modified version of Luo-Rudy model phase II [7,8] for ventricular action potential and DiFrancesco-Noble model [9,10] for Purkinje action potential. We considered a fiber of 100 Purkinje cells connected through a Purkinje-ventricular resistance (R_{PVJ}) to central ischemic ventricular cells (100), then to border zone ischemic cells (100) and then to normal ventricular cells (100), as shown in figure 1. 1B ischemic conditions were reproduced by altering electrophysiological parameters as observed experimentally, and gradients were gradual in the border

zone from the 1B ischemic values to the normal values (see [11] for details). The calculation of the Safety Factor (SF) allowed us to quantify the safety in conduction as cellular uncoupling was increased. The model was stimulated with 11 pulses in the cell #0 of Purkinje fiber with an amplitude of 1.2 times the diastolic threshold and 2 ms in duration, the 11th pulse was considered for analysis.

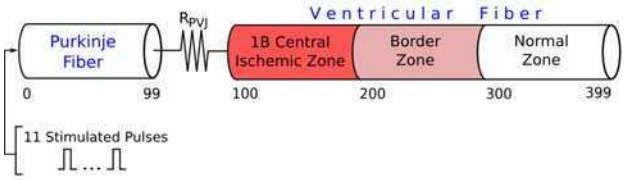

Figure 1. 1D Model of a Purkinje fiber connected to ventricular cells through a Purkinje-ventricular resistance (R_{PVJ}). The Purkinje fiber was composed of 100 cells (1.5 cm) and the ventricular fiber of 300 cells (3 cm).

Subsequently, we adapted the model to a ring configuration. A Purkinje fiber was connected to a ventricular fiber through two Purkinje-ventricular junctions, R_{PVJ1} and R_{PVJ2}. The ventricular fiber was composed of three parts, including ischemic (300 cells), border (100 cells) and normal (100 cells) zones as shown in figure 2.

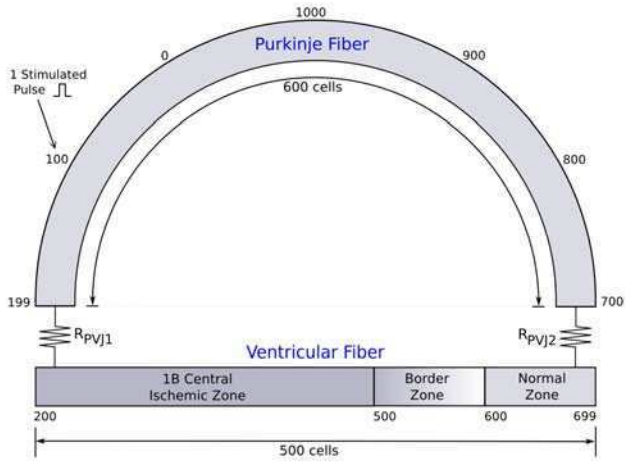

Figure 2. Ring Model composed of a Purkinje fiber of 9 cm (600 cells) and a ventricular fiber of 5 cm (500 cells). The fibers were coupled with two Purkinje-ventricular junctions (R_{PVJ1} and R_{PVJ2}).

Cellular uncoupling observed during 1B phase of ischemia was simulated by altering the gap junction resistance of ventricular cells (R_{endo}). R_{PVJ1} connected the Purkinje fiber to the ischemic ventricular zone and was varied in a range of 16 to 40 $\Omega \cdot cm^2$. R_{PVJ2} coupled the Purkinje fiber to the normal zone of the ventricular fiber and was fixed to 16 $\Omega \cdot cm^2$ producing a delay of 2.2 ms in the conduction from Purkinje to ventricle. The $[K^+]_o$ was varied from 11 to 12 mmol/L in the 1B ischemic zone. The Purkinje fiber was stimulated with 1 pulse in cell #100 of 1.2 times the diastolic threshold in amplitude and 2 ms in duration.

3. Results and discussion

Our results showed that propagation block can be elicited for low and high values of ischemic cellular uncoupling as long as hyperkalemia is severe and uncoupling between Purkinje and the ventricular fiber is also high. Additionally, intermediate coupling of ischemic ventricular cells favors AP propagation. To analyze the safeness in conduction we evaluated the SF in the different cells of the fiber, as shown in figure 3. Under conditions of high ventricular hyperkalemia ($[K^+]_o$ = 11.5 mmol/L) and high Purkinje-ventricle uncoupling (R_{PVJ} = 24 $\Omega \cdot cm^2$) the SF yielded 2.5 in Purkinje cells, but near the Purkinje-ventricular junction (PVJ), SF presented a peak. In the ischemic ventricular cells, for intermediate values of R_{endo}, SF varied from 1.5 to 1.6, so that conduction was successful (SF > 1). In the border zone, SF increased and decreased in a nonlinear manner. Finally, in the normal ventricular zone, SF was constant with a value of 1.8. However, for low and high values of R_{endo} (5 $\Omega \cdot cm^2$ and 39 $\Omega \cdot cm^2$ respectively) in the ischemic zone, conduction block from Purkinje to ventricular was observed (SF < 1).

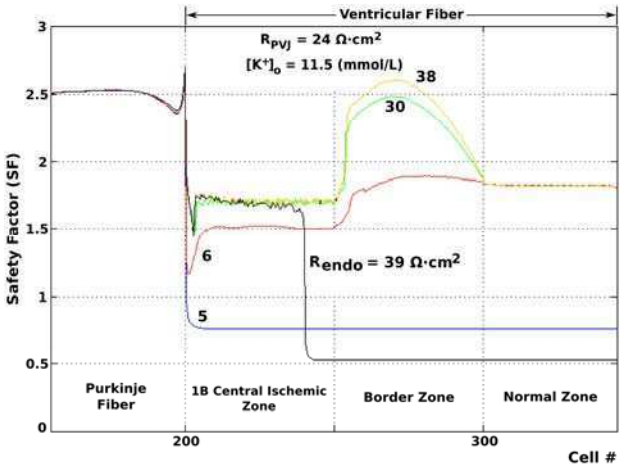

Figure 3. SF calculated for Purkinje to ventricular conduction (P-V). The coupling of ventricular cells (R_{endo}) was varied in the range of 5 to 40 $\Omega \cdot cm^2$.

Similar results were obtained in [12], in experiments with mice. Morley et al. found that a reduction in coupling of ventricular myocardium provoked propagation across the Purkinje-ventricle junction. Also,

Rohr et al. [13] observed that the spatially uniform reduction of electrical coupling in neonatal rat ventricular myocytes produced successful conduction.

To further analyze the effects of uncoupling and hyperkalemia, a set of simulations was conducted where R_{endo}, R_{PVJ} and $[K^+]_o$ were modified. Their effects on conduction from Purkinje to ventricle (P-V conduction) and from ventricle to Purkinje (V-P conduction) are summarized in Table 1. The range for conduction strongly depends on $[K^+]_o$ and R_{endo} in the 1B ischemic zone, and on the value of coupling between Purkinje and ventricle (R_{PVJ}). $[K^+]_o$ affects the range of conduction from Purkinje to ventricle for low and high values of R_{endo}. The increase of $[K^+]_o$ reduces the conduction range. If we consider ventricular to Purkinje conduction, $[K^+]_o$ has an influence only for high values of R_{endo}. The influence of R_{PVJ} is more evident for low values of R_{endo}. When the model was stimulated in cell #399 of the ventricular normal zone, conduction block was observed only for high values of resistance in the 1B ventricular ischemic zone. The increase of coupling between Purkinje and ventricle had little effect in the range of conduction from ventricle to Purkinje. With respect to the $[K^+]_o$ of the 1B ischemic zone, a greater concentration leads to a reduction in the conduction range.

	Range of P-V Conduction		Range of V-P Conduction	
R_{PVJ} ($\Omega \cdot cm^2$) / $[K^+]_o$ (mmol/L)	16	24	16	24
11.5	5-38	6-38	5-38	5-38
11.6	5-30	7-30	5-30	5-30
11.7	6-20	9-19	5-20	5-20
	R_{endo} of 1B Ischemic Zone ($\Omega \cdot cm^2$)			

Table 1. Conduction ranges obtained when the 1D model of figure 1 was stimulated in cell #0 of Purkinje fiber (P-V conduction) and in the cell #399 of ventricular fiber (V-P conduction).

In the ring model, unidirectional block was obtained under certain 1B ischemic conditions in Purkinje to ventricular conduction (P-V) and in ventricular to Purkinje propagation (V-P), both under the same 1B ischemic conditions, and constant values for $[K^+]_o$ and R_{PVJ1}. Thus reentry was obtained for a range of R_{endo} comprised between 5 and 8 $\Omega \cdot cm^2$ when severe hyperkalemia was considered (from 11.5 to 11.7 mmol/L) and R_{PVJ1} was established at 24 $\Omega \cdot cm^2$. The stimulated pulse applied to cell #100 of the Purkinje fiber propagated in two directions, anterogradely (towards R_{PVJ1}) and retrogradely (towards R_{PVJ2}). As shown in figure 4, the anterograde propagation was blocked near the Purkinje-ventricular junction (arrow A, figure 4). The retrograde propagation (arrow B, figure 4) reaches the ventricular normal zone, border zone and 1B ischemic zone (arrow C, figure 4), and then the Purkinje fiber (arrow D, figure 4), leading to a reentrant circuit. Table 1 summarizes the conditions for R_{PVJ1} under which we obtained unidirectional block (blockade in P-V conduction and propagation in V-P conduction) which induce reentrant activity in the developed model. Increasing R_{PVJ1} widened the range of R_{endo} for which reentry was originated. In fact, as happened in the fiber analysis (see table 1), an increase in R_{PVJ1}, increased the probability of conduction block, which leads to reentry in the ring model.

In pairs of isolated rabbit Purkinje cells coupled by a variable resistance to ventricular myocytes, Huelsing and Spitzer [6] found that conduction block occurred at lower values of coupling resistance during P-V conduction than in the case of V-P conduction. Our results show a similar tendency but considering the impedance of ventricular tissue. In fact, we obtained conduction block at low values of coupling resistance between 1B ischemic ventricular cells in P-V conduction, whereas in V-P conduction, conduction block was observed only at higher values of impedance of 1B ischemic ventricular tissue.

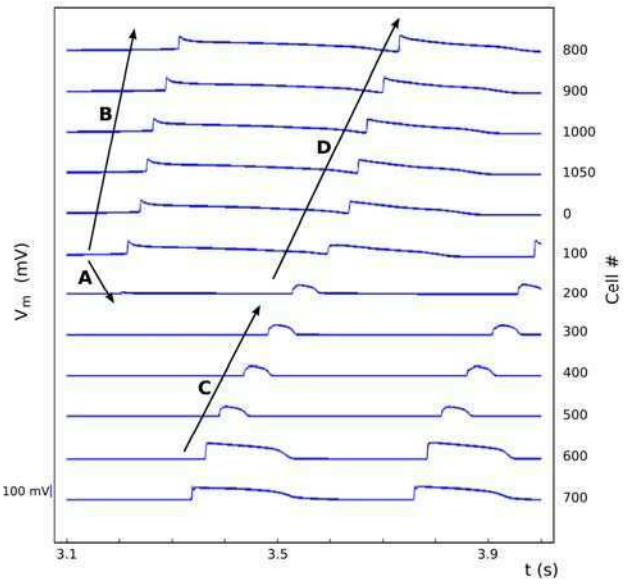

Figure 4. Reentrant activity observed in the ring model of the Purkinje fiber coupled to 1B ischemic ventricular fiber through R_{PVJ1}.

4. Conclusions

In conclusion, cellular uncoupling during 1B ischemia and hyperkalemia are crucial factors in the generation of propagation block, which are precursor of reentrant

activity.

Acknowledgements

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