Dispersion of Refractoriness in a Simulated Ischemic 2D Tissue and Implications in Vulnerability to Reentry

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Abstract

During the acute phase of myocardial ischemia, electrophysiological changes and heterogeneities predispose the heart to arrhythmogenic reentrant excitation. In this computational work we analyze the role of dispersion of refractoriness on reentry generation in a two-dimensional sheet of ischemic tissue at different stages after the onset of ischemia. A realistic model of regional ischemia was used basing our simulations on a modified version of the 2000 Luo-Rudy action potential model. Our results are consistent with experimental studies in which vulnerability to ventricular arrhythmias has an unimodal behavior in the acute phase of myocardial ischemia. We also observed that dispersion of refractoriness was necessary for reentry to ensue, but its dispersion degree did not correlate with vulnerability. Thus, other ionic factors such as axial currents must be involved in the modulation of the vulnerability to reentry.

1. Introduction

During the acute phase of myocardial ischemia, electrophysiological changes predispose the heart to the occurrence of ventricular arrhythmias [1]. Two phases of ventricular fibrillation (VF) incidence have been documented, peaking the first phase before minute 10 after coronary occlusion [2]. Much attention has been paid to the generation of this lethal arrhythmia and there is substantial experimental evidence to support the belief that reentrant excitation is an important mechanism, which may lead to disorganized electrical activity and thus is considered as a precursor to VF.

Two conditions are required to initiate reentry: a trigger, and the substrate nesting the reentrant pathway. Focusing this second factor, it has been well established that electrophysiological alterations occurring during regional ischemia set the stage for reentry [1]. Indeed metabolical and physiological changes, including hypoxia, hyperkalemia and acidosis, arise in the ischemic tissue [3,4] and thus heterogeneities in electrical properties, such as refractoriness, contribute to reentry generation. Many experimental [5,6] and computational studies [7,8] have been undertaken to evaluate the effects of dispersion of electrophysiological conditions within the heart muscle on the vulnerability to reentry.

The aim of this computational work was to analyze the role of dispersion of refractoriness on vulnerability to reentry at different stages after the onset of ischemia. Mathematical models were used to simulate the electrical activity of a virtual sheet of regionally ischemic myocardial tissue.

2. Methods

The electrical activity of myocardial cells was simulated using a modified version of the 2000 Luo-Rudy action potential model [9], in which the formulation of the ATP sensitive potassium current ($I_{K(ATP)}$) was included [3].

To simulate ischemic conditions, hyperkalemia, hypoxia and acidosis were considered at different stages after the first 10 minutes of coronary occlusion. Firstly, the extracellular potassium concentration ($[K^+]_o$) was linearly varied from its normal value 4.5 mmol/L at minute 0 until 12.5 mmol/L at minute 5, according to experimental recordings [4]. Secondly, hypoxia was simulated by increasing linearly intracellular ADP concentration ($[ADP]_i$) and decreasing intracellular ATP concentration ($[ATP]_i$) and thus increasing the fraction of open $I_{K(ATP)}$ channels from 0% at minute 0 to 0.7% at minute 10 [3]. Lastly, intracellular and extracellular acidosis were mimicked by scaling calcium and sodium currents by a factor f_{pH} in the range of 1-0.75 from minute 5 to minute 10 respectively [10].

We simulated the electrical activity of an anisotropic 2D sheet of 5.5cm×5.5cm subject to regional ischemia. A central ischemic zone (CZ) and a ring-shaped electrophysiological border zone (BZ) were considered.

The dimensions of these zones and the linear variation of the electrophysiological parameters within the BZ respond to realistic experimental observations [1,11] (See [10,12] for details).

We followed an S1-S2 stimulation protocol applied at the bottom edge of the tissue. Both pulses were rectangular 2 ms in duration and 1.5 times diastolic threshold. S1 was delivered after a 50 ms stabilization period, and the premature stimulus S2 was delivered at different coupling intervals (CIs). The vulnerable window (VW) for reentry was defined as the interval of CIs yielding reentrant activity in the tissue.

The product of sodium channels inactivation gates j and h was used as an indicator for refractoriness. The estimated refractory period was calculated as:

$$T_{hj=0.1} - t_{(max\ der)} \quad (1)$$

Where $T_{hj}=0.1$ stands for the instant of time where the product hj yields 0.1 and $t_{(max\ der)}$ is the instant of maximum derivative during the depolarization phase.

Refractory periods (RPs) were also measured in the central fiber of the tissue by stimulating prematurely in the zone where the RP was seeked. The RP was defined as the minimum CI leading to AP propagation.

3. Results and discussion

Our results are consistent with experimental studies in which vulnerability to ventricular arrhythmias has an unimodal behavior in the acute phase 1A of myocardial ischemia. Several authors have suggested that the likelihood of VF peaks before 10 minutes [2]; our results give a theoretical frame and support this hypothesis. We obtained that for early stages of ischemia (prior to minute 6.5) no reentry was originated, then the width of the vulnerable window (VW, i.e. time interval of the reentrant premature stimulus), widens and reaches the maximum value (58 ms) for minute 8. Finally the VW decays again as ischemia conditions are worsened, as shown in figure 1.

Depending on S_2 timing and on the ischemic conditions of the tissue, different patterns of propagation were encountered. Firstly, if S2 was delivered too early, with a CI lower than 170 ms, no propagation succeeded as cells at the stimulus site had not yet recovered from refractoriness, regardless of the central ischemic conditions. Then, for larger CIs the three following behaviors observed: collision, reentry and bidirectional block (BDB). Finally, for a much larger CI, late enough depending on central ischemic conditions, S2 propagated throughout the sheet, as excitability was recovered again.

In figure 2, patterns of activation of a figure-of-eight reentry are shown. This reentrant excitation was obtained after a premature S2 stimulation included in the VW, eight minutes after the onset of myocardial ischemia.

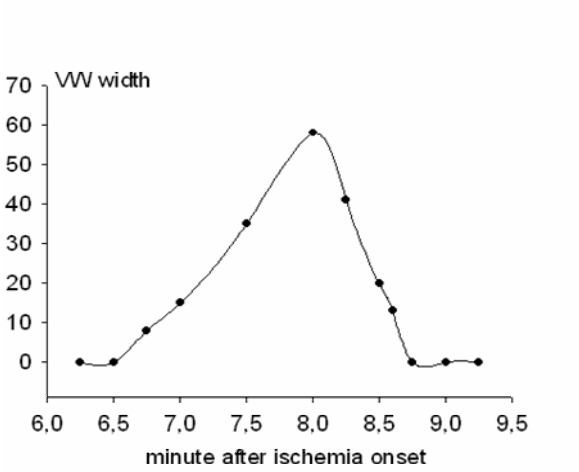

Figure 1. Width in ms of the vulnerable window for reentry at different minutes after the onset of myocardial ischemia.

A conduction block was observed in the proximal side of the CZ. The wavefront surrounded the refractory ischemic tissue via two alternative pathways invading retrogradely the distal CZ after this zone had recovered from refractoriness. Unidirectional block (UDB) and thus reentry was established. Similar patterns have been experimentally observed [1] in pig ischemic hearts where reentry war precursor to ventricular fibrillation.

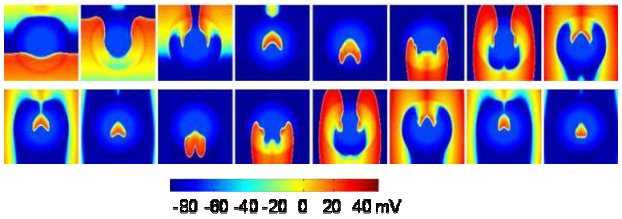

Figure 2. Figure-of-eight reentry in the simulated tissue after a premature stimulus at minute 8 after the onset of myocardial ischemia. Each panel represents a voltage snapshot and is 50 ms separated from the following one.

We also estimated refractory periods within the tissue, in order to evaluate their dispersion and repercussion on the probability of reentry generation. The regional gradients in repolarization reproduced by our simulated ischemic tissue correlate with arches of conduction block around which reentry circulates, as reported in experimental studies [5,13]. Computational and theoretical studies have also shown the importance of PR dispersion in the susceptibility to reentries [14].

In the present work, refractory periods at the different stages of ischemia showed that dispersion of

refractoriness was a necessary condition for the tissue to nest reentry. As depicted in figure 3 panel A, eight minutes after the onset of myocardial ischemia (right), refractoriness map was drastically more abrupt than in early stages (minute 4, left) where no reentry was initiated. This observation is in accordance with experimental and theoretical studies in which a threshold in dispersion of refractoriness is needed for arrhythmogenic processes to arise [7,6].

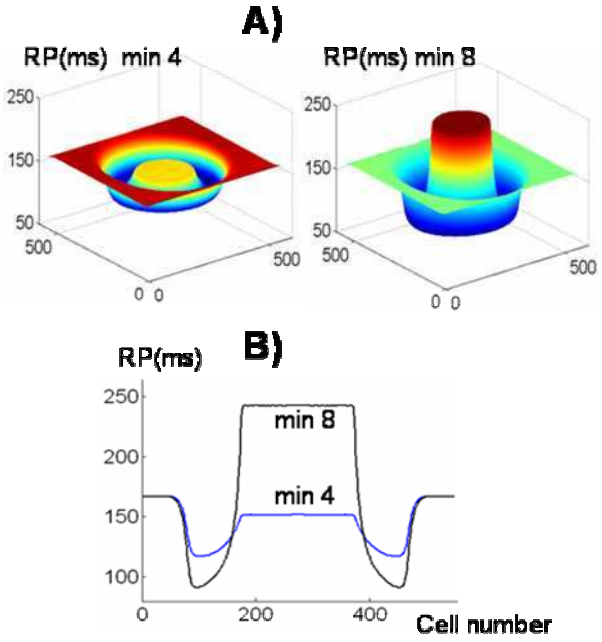

Figure 3. A) Spatial distribution of the value of the refractory period after the basic stimulus. Two conditions of ischemia are represented: minute 4 (left) and 8 (right). B) Spatial distribution of the value of the refractory period after the basic stimulus according to minutes 4 and 8 along the central fiber of the tissue.

Aiming at correlating dispersion of refractoriness with the probability of reentry generation, we calculated the maximum difference between the measured RP in the different zones of the tissue, after the basic stimulation at different stages of ischemia. As represented in the top of figure 4, as ischemia progressed, dispersion of refractoriness followed an increasing evolution from 84 ms at minute 6.5 to 214 ms at minute 8.75. and the correlation factor yielded 0.97. This monotone increase did not present an unimodal behavior as did the VW for reentry. Indeed, the correlation between dispersion of refractoriness and the VW, shown in the bottom of figure 4, poorly yielded 0.03. Similar theoretical results were obtained by Qu and coworkers [15].

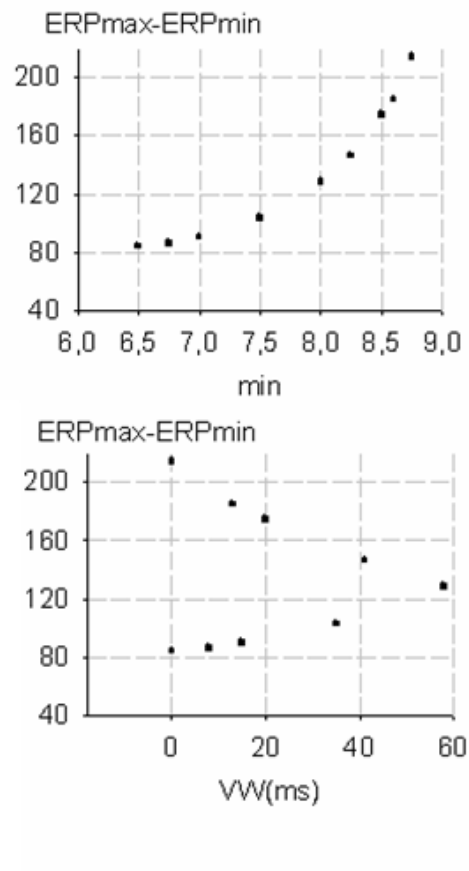

Figure 4. Calculated dispersion of refractoriness in the central fiber for different minutes of ischemia (top) and as a function of the width of the vulnerable window for reentry (bottom).

Although many authors have experimentally and theoretically demonstrated the existing correlation between dispersion of APD or RP and arrhythmogenic processes [7,8,14] it should be pointed out that this indicator has been evaluated in different ways in the scientific literature, also experimental and tissue conditions are to be considered. For instance, Clayton and Golden demonstrated in a 2D simulated tissue how an increase in the standard deviation of APD led to an increase of the susceptible window for reentry [8]. Similarly, Namba and coworkers theoretically showed how higher heterogeneities in RP within a 2D tissue implied a wider VW for spiral reentries [14]. Ischemia was not modelled in the aforementioned studies.

On the other hand, Laurita and coworkers [16], hypothesized that unbalance in the ionic processes reflected in the source-sink relationship has an important role in UDB and thus reentry generation. The lower

source-sink relationship, the less dispersion of refractoriness is required to provoke conduction block. This is in accordance with our results, as BDB is favored under severe conditions of ischemia, where the source-sink relation-ship is further compromised.

Other authors sustain a non-linear relationship between dispersion of refractoriness and probability of arrhythmia [17,18,6]. In this way, Roger and coworkers [17]obtained reentries in a 3D model of the heart surface, in wich the geometric complexity was enough to originate reentry. Other authors [18,6] experimentally observed that the reduction of APD or ERP dispersion increased the probability of arrhythmias. Controversial results can be found in the literature indicating that not only the electrical state of the cell but also other factors, such as ionic processes and axial currents, are involved in the block of AP propagation and thus in reentry generation.

4. Conclusions

Our results suggest that dispersion of refractoriness is necessary for reentry to ensue, but its dispersion degree does not correlate with vulnerability. Thus, other ionic factors such as the source-sink relationship and thus axial currents must have an important role in the modulation of the vulnerability to reentry.

Acknowledgements

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