Effect of Regional Ischemia in Arrhythmia Vulnerability for Heterogeneous Transmural Cardiac Wall: A Simulation Study

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Abstract

It is well known that ventricular fibrillation (VF) is a major cause of sudden cardiac death in developed countries. Myocardial regional acute ischemia constitutes a heterogeneous substrate which tends to destabilize the electrical depolarizing wave front, thus favouring VF. Functional re-entry in the transmural wall has been hypothesized as the underlying mechanism of VF. In this work, we have theoretically studied (using computer simulations) the temporal evolution of the vulnerable window (VW) for re-entry in an acutely ischemic virtual tissue which represents the transmural ventricular wall. The model predicts that the VW for re-entry has biphasic behaviour during acute myocardial ischemia, with re-entry paths comprising endocardial, midmyocardial and epicardial tissue.

1. Introduction

Ventricular tachycardia and ventricular fibrillation are known to be two types of cardiac arrhythmias that frequently lead to sudden cardiac death [1]. These arrhythmias are normally due to re-entry, a phenomenon which involves self-perpetuating circulating electric wave fronts within the ischemic ventricular muscle. When re-entry occurs, electric activity travels around functional singularity phase [2]. In this case, the initial propagating wave front encounters an area of refractory tissue (functional block), propagates around it via alternative pathways, retrogradely invades the zone of block if the tissue has recovery its excitability, and finally emerges as a reentrant wavefront at the site of origin [3]. The general effects of ischemia on myocardium include those which are secondary to a diminished local supply of substances such as oxygen and metabolites as well as changes resulting from the impaired diffusion of substances such as lactic acid and electrolytes from the poorly perfused ischemic tissue to the general circulation [4].

Indeed, it is know that acute myocardial ischemia elicits many biochemic changes that influence the electric signal of cardiac myocytes [5;6].

In this work, we study the time-course of the vulnerable window to re-entry (VW) using a detailed model of acute regional ischemia in a 2D virtual transmural heterogeneous wall (comprising endocardial, midmyocardial and epicardial zones) in which the different ischemic zones are realistically modelled.

2. Methods

In order to simulate re-entry in a 2D heterogeneous virtual wall cardiac, the electrical activity of cells is described using the biophysically detailed Luo-Rudy model of action potential [7;8]. The heterogeneity of the ventricular wall is including in the model through the transient outward potassium current $\boldsymbol{I_{to}}$ [9] and differences in the slow delayed potassium rectifier current $\boldsymbol{I_{Ks}}$ [8;10]. Acute ischemia was reproduced by means of its three principal components. Firstly, hypoxia was considered by partially activating the ATP-sensitive K^+ current (I_{KATP}), using mathematical formulation of Ferrero Jr. et al [11]. The intracellular values of ATP an ADP were tuned to yield a fraction of open channel of 0.1% [11;12]. Secondly, hyperkalemia was simulated by elevating extracellular K^+ concentration ($[K^+]_o$). In particular $[K^+]_o$ was set to a value in the range 4.5-12.5 mmol/L [12;13]. Finally acidosis was taken into account by its effect on the Na^+ and Ca^{2+} currents. Hence, the fast inward Na^+ current and the Ca^{2+} current through the L-type channel were affected for a factor f_{pH} comprised between 1.0-0.65 [14] (see Fig 1) .

If cardiac tissue is assumed to be a uniform functional synctium (a clump of cells which act together as a functional unit) then the cable equations as in [15] can be extended to describe spatially extended 2D excitable media:

$$\vec{\nabla} \cdot D\vec{\nabla}\Phi_i - \frac{I_{ion} + I_{applied}}{C_m} = \frac{\partial V_m}{\partial t} \quad (1)$$

In our simulations, we considered a 2D virtual tissue which simulates a 30x15 mm rectangular anisotropic transmural wall subject to regional ischemia. The geometrical distributions of heterogeneity is compound for epicardial band (20% wall), two cluster of M cell (35% wall) (see Fig. 1) [16]. Ignoring the microscopic nature of cell structure in the heart, the tissue which responds to a reaction-diffusion-type partial differential equation as follows:

$$\frac{1}{s_v}\left(\frac{1}{\rho_x}\frac{\partial^2 V_m}{\partial x^2} + \frac{1}{\rho_y}\frac{\partial^2 V_m}{\partial y^2}\right) = C_m \frac{\partial V_m}{\partial t} + \sum I_{ion} + I_{applied} \quad (2)$$

where S_v is the surface-to-volume ratio, ρ_x and ρ_y are the cellular resistivities in the transversal and longitudinal directions, respectively.

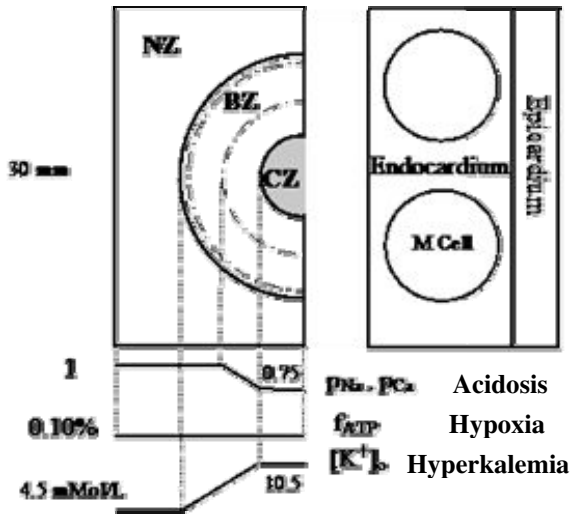

Figure 1. Left: virtual regional ischemic tissue (NZ: normal zone; BZ: border zone; CZ: central zone). Right: geometrical distribution for heterogeneity wall

For computational purposes, the tissue was discretized in 100x100 μm patches. Equation (2) was solved using the operator-splitting method. The resultant diffusion equation was solved using an alternating-direction implicit scheme, while for the reaction equation a implicit Euler Method was employed. A time-step of 18 μs was chosen in order to avoid numerical artefact in model solver. No-flux boundary conditions were used. As for cellular resistivities, appropriate values were chosen to obtain a longitudinal conduction velocity of 50 cms^{-1} and transversal of 13 cms^{-1} (under normal conditions) with an anisotropic velocity ratio 4:1 [17]

The first basic stimulus (S1) was applied after 50 ms for electrical variable stabilization. The second stimulus (S1), which mimics a premature stimulus, was applied with suitable coupling interval (CI) for tissue. The duration of pulse was 2 ms, and amplitude was two fold the diastolic threshold in the normal tissue.

For the simulations displayed in this work, the CAMAEC simulation system was used, developed by the High Performance Networking and Computing Group (GRyCAP), from the Polytechnical University of Valencia [18].

3. Results

In Figure 2 (frames separated 80 ms), the spatial and temporal evolution of the wavefront potential for the minute seven of ischemia is shown, the tissue was stimulated with S1-S1 protocol and a CI varying from 170 to 190 ms, the second stimulus it penetrates for the epicardium (frame 3,4) and it generates a wavefront that is blocked in the proximal area of the lesion corresponding to border zone, eliciting a lobular wave that rotates counterclockwise from the epicardium to endocardium. The functional tip remains within the central ischemic zone in all the simulations, the black small ellipse in the fig 2 (frame 5). The tip movement is nonstationary in the lesion zone indicating meander of spiral core via destabilization of conduction block (Hopf bifurcation of dynamical system).

Table 1 resumes the width of vulnerable window (the time interval during which single extra stimulus can initiate self-sustaining propagation) for different minutes of ischemia studied.

In the seventh miniute of simulated ischemia, a spiral wave was found only in an interval of 5 ms from CI 170 to 175 ms. The width of VW increased with extracellular potassium concentration. The VW further increased to 20 milliseconds in t=8 minutes. It then plateaus, and abruptly decreases to zero in the ninth minute.

Table 1. Vulnerable window in ischemic wall.

Ischemia Minute	Width VW
6,5	0
7	5
7,5	15
8	20
8,5	20
9	0

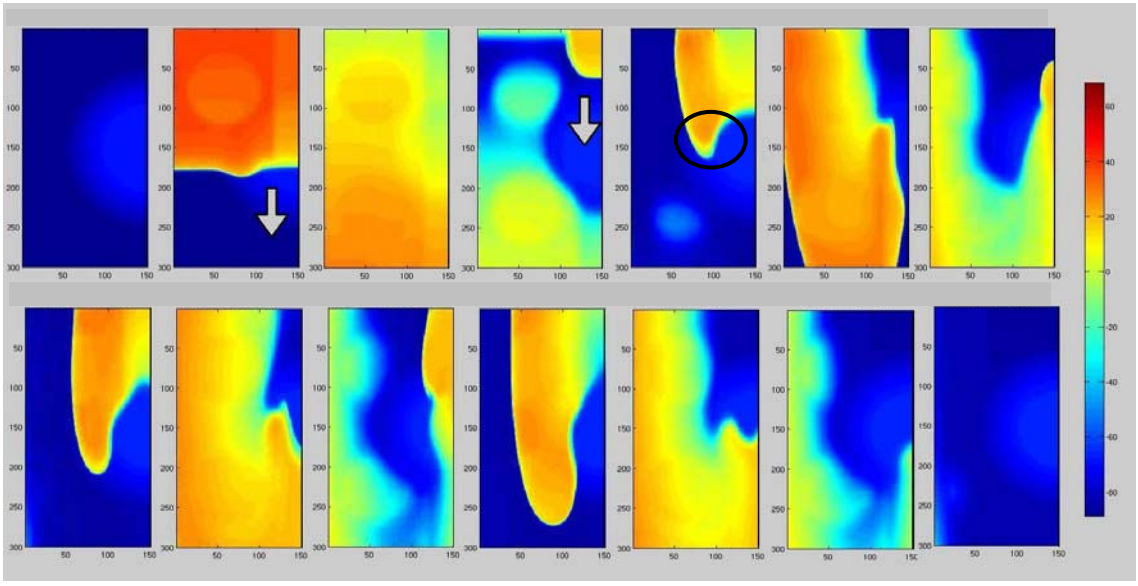

Figure 2. Transmural re-entry initiated by S1-S1 protocol line stimulus after 800 ms in ischemic regional wall.

Figure 3 shows the vulnerability to re-entry (y_axis), indicated by the VW, versus the minute of ischemia simulated (x-axis). The upper trace shows the histograms and lower part logistic approximation for dates in percentile. As can be seen, a sharp demarcation between near zero and near unity probabilities occurred in seven and half eighth minutes of ischemia in transmural wall. One simple classification scheme based of this probability function predicted 70% of re-entry events occurred in this range of parameters of simulated ischemia. The time-course of the VW was well adjusted to a logistic distribution with m=12.5206, sigma=68.5186 an log likelihood of -90.3555

4. Discussions and conclusion

It is well know that acute ischemia depresses tissue excitability and conduction velocity more rapidly in epicardium than in the endocardium, therefore creating transmural dispersion in tissue excitability [19]. The rotors in wall transmural are difficult to manage of way experimental, because the impossibility of tools of visualization for the cardiac wall, it is necessary to come to surgical portions of ventricles of mammals for study wavefront movement in ischemic wall [20].

The marked dependence of recovery of excitability on the resting membrane potential in partially depolarized ischemic transmural wall is probably the most important determinant for the occurrence of slow conduction and conduction block in the acute phase of ischemia.

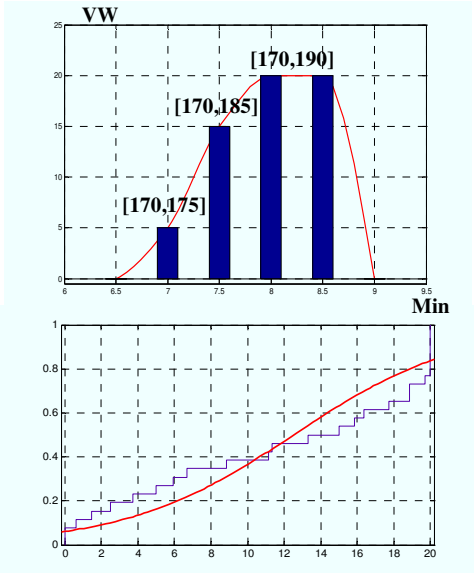

Figure 3. Histogram of VW (upper traces) and Distribution approximation of dates in percentiles (details in text)

This study shows how the greater epicardial sensitivity to ischemia, the heterogeneity in tissue excitability, and the conduction delay combined to provide all the necessary conditions for the initiation, maintenance and terminations of transmural re-entry during regional acute ischemia [19;21].

The differential responses in the border zone of epicardial tissue created the functional pathway for spiral re-entry during regional ischemia. The dynamic changes in activations produced for elevated concentration of extracellular potassium forms vulnerable windows for settling lobular rotating waves [22].

In conclusion, the model predicts that the VW for re-entry has biphasic behaviour during regional acute myocardial ischemia in cardiac transmural wall and it is approximate for a logistic distribution.

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