

# M-cell Heterogeneity Influence in Arrhythmic Pattern Formation in Sub-epicardial Regional Ischemia: a Simulation Study

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## Abstract

Ventricular arrhythmias are often triggered by acute myocardial ischemia. The occurrence of lethal arrhythmias is normally related with myocardial injury, alterations of ionic conductances and metabolite concentrations. Ischemia alters the myocardium heterogeneously, differently affecting epicardium, M-cells and endocardium. In this computational study, we calculate the vulnerability to reentry during different stages of regional sub-epicardial ischemia in dissimilar island configurations of M cells in the myocardial wall (*Antzelevitch's* hypothesis). The main components of ischemia (hypoxia, acidosis and hyperkalemia) were considered in the model. The tissue comprises 150x300 cells, which include different islands of M cells up to 55% tissue area, 20% for epicardial cells and the rest of endocardial zone. The results of the model predict that the vulnerable window for re-entry has a logistic behaviour during sub-epicardial ischemia, with re-entry paths comprising midmyocardial islands of tissue.

## 1. Introduction

Sudden cardiac death and ventricular fibrillation are often triggered by acute myocardial ischemia [1]. Presence of one can precipitate and perpetuate the other. The occurrence of potentially lethal arrhythmia is the end result of a cascade of pathophysiological abnormalities from complex interactions between coronary vascular events, myocardial injury, alterations in energy balance and metabolite concentrations [2;3]. Cardiac excitation can be viewed as an electrical wave, with a wavefront corresponding to action potential (AP) upstroke (phase 0) and wave back (phase 3) [4]. Wave break (phase singularity) occurs in the intersection of the depolarizing wavefront and refractory wave tail. Histological and pathologic tissue heterogeneity due to structural and electric behaviour associated with cardiac wall or disease greatly enhances the probability that physiological triggers will induce wave break and

initiate re-entry leading ventricular tachycardia (VT) or ventricular fibrillation (VF) [5;6].

In the presence of structural or electrophysiological heterogeneity [7] in the ischemic heart (biochemically altered) [6;8], a premature beat can sometimes induce wavebreaks. Triggers of VF occur in the border zone of regional ischemic heart. Dynamic properties of the cardiac AP also have a major influence on the vulnerability for re-entry formations in the setting of ischemia parameters.

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, M-cell 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 [9;10]. The heterogeneity of the ventricular wall is included in the model through the transient outward potassium current  $I_{to}$  [11] and differences in the slow delayed potassium rectifier current  $I_{Ks}$  [10;12], the conductance of three cell types of wall change according to the ratio 23:7:15 respectively. In our simulations, we considered a 2D virtual tissue which simulates a 30x15 mm<sup>2</sup> rectangular anisotropic transmural wall subject to regional sub-epicardial ischemia. The geometrical distributions of heterogeneity comprises an epicardial band (20% wall), and different islands of M cell (55% in band, 35% in two clusters, one cluster 17%, ) and control no M cell endocardium at rest wall (see Fig. 1) ubiquitous in diverse localizations of the virtual wall [13;14]. The possible diversity of M-cell island/band widths is covered in the literature [15;16].

Acute ischemia was reproduced by means of its three principal components. Firstly, hypoxia was considered by partially activating the ATP-sensitive K<sup>+</sup> current ( $I_{KATP}$ ), using mathematical formulation of

Ferrero Jr. et al [17]. Secondly, hyperkalemia was simulated by elevating extracellular  $K^+$  concentration ( $[K^+]_o$ ). In particular  $[K^+]_o$  was set to a value in the range 4.5-12.0 mmol/L [18]. Finally acidosis was taken into account by its effect on the  $Na^+$  and  $Ca^{2+}$  currents. If cardiac tissue is assumed to be a uniform functional syncytium, then the cable equations 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. Ignoring the microscopic nature of cell structure in the heart, the tissue 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,  $\rho_x$  and  $\rho_y$  are the cellular resistivities in the transversal and longitudinal directions, respectively. For computational purposes, the tissue was discretized in 100x100  $\mu m$  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. 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 [19]. 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 [20].

### 3. Results

In Figure 2 (frames separated 150 ms), the spatial and temporal evolution of the membrane potential for the eight and a half minute of ischemia is shown for the different distributions of M cell considered. The tissue was stimulated with S1-S2 protocol and a CI varying from 170 to 220 ms, the second stimulus penetrates in the tissue (frame 2) and block in medial ischemic zone generating a spiral wave that rotates counterclockwise from epicardium to endocardium. Frame 3 shows the reversal front moving from distal to proximal ischemic lesion, and the slowing down of the wavefront can be

noted in central zone, in the simulations that include island of M cell. Frame 4 shows functional termination of wavefront movement in the distal zone of lesion. The delay of wavefront circulations is due the dispersion of repolarization mediated for M cell distribution in virtual tissue.

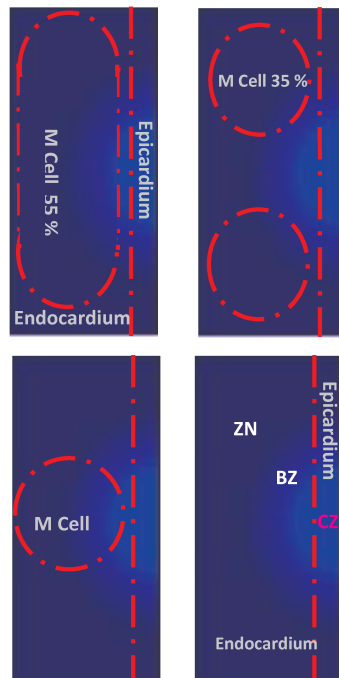


Figure 1. Virtual regional ischemic tissue NZ: normal zone; BZ: border zone; CZ: central zone. Geometrical distribution for heterogeneity wall of M cell islands

The functional tip remains within the central ischemic zone in all the simulations, the spiral wave movement is non-stationary in the lesion zone indicating meander of spiral core via destabilization of conduction block (Hopf bifurcation of dynamical system). It can be noted that alteration of repolarization wavefront is not noticeable in the control simulation increasing the potential role of M cell in alteration of recovery of virtual tissue. Table 1 summarizes the width of the vulnerable window for different minutes of ischemia studied and different intramural distributions of M cell. In the eighth minute of simulated ischemia, a spiral wave was found only in an interval of 7 ms from CI 170 to 177 ms. the width of VW increased with extracellular potassium concentration. The VW further increased since 7 to 27 milliseconds in  $t=8.25$  to 8.75 minutes. It abruptly decreases to zero in the ninth minute.

Table 1. Vulnerable window in ischemic wall for M-cell distributions utilize in simulation.

Insult minute	VW 55% M cell	VW 35% M cell	VW 17% M cell	VW no M cell
7,5	0	0	0	0
8	7	7	7	5
8,25	10	12	11	10
8,5	17	13	15	10
8,75	21	17	27	12
9,0	0	0	0	0

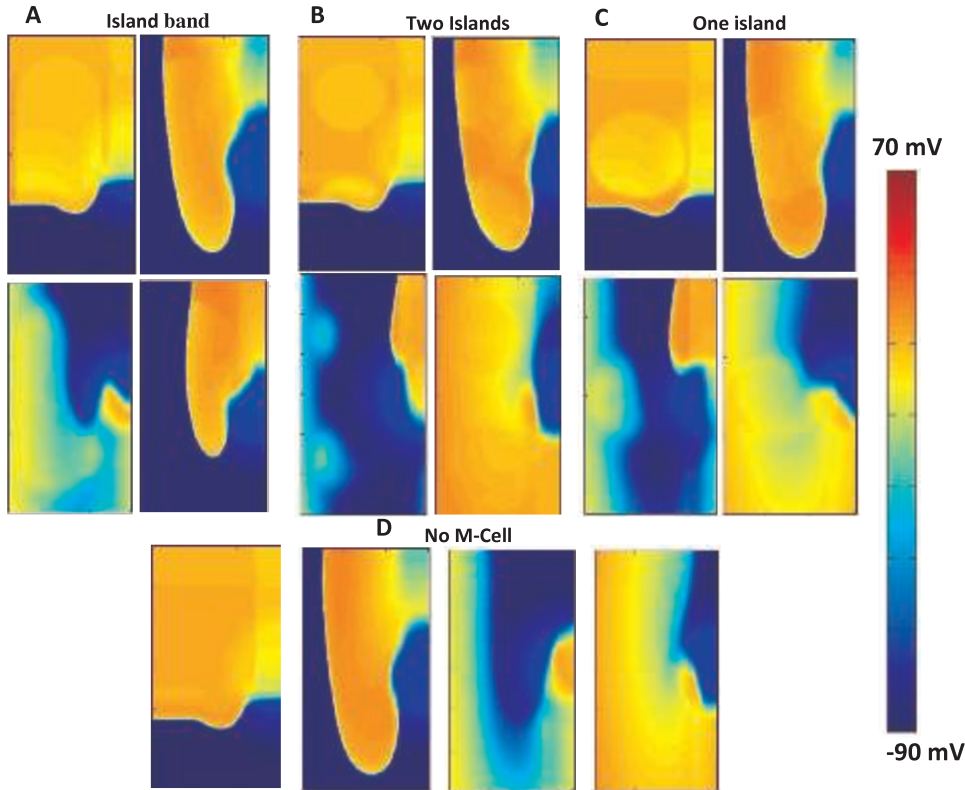


Figure 2. Transmural re-entry after 600 ms in ischemic regional wall. Photograph in 150, 300, 450 and 600 ms respectively for all distributions of M-cell. A. Island band; B. Two clusters; C. One Cluster and D. Control no M cell distribution in the virtual cardiac wall.

Figure 3 shows the vulnerability to re-entry (z-axis), indicated by the VW, versus the minute of ischemia simulated (y-axis) versus M cell distributions (x-axis, front control and backward 55% M Cell). The frontmost trace shows the histograms to control and little variations of interval of VW is observed. The central VW functions show dissimilar time interval of VW in the last minute simulated, the M cell in the middle zone and the severity of ischemic parameters are guilty of augmented probability of reentry in 100% in this minute. It can be seen that a sharp demarcation between near zero and near unity probabilities occurred in eight and 8.75 minutes of ischemia in the 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  $m=19.42$ ,  $\sigma=59.34$  an log likelihood of  $-118.38$  to band distribution of M cell in virtual tissue

#### 4. Discussions and conclusion

The acute ischemic lesion sub-epicardial differently depresses the tissue excitability and conduction velocity more rapidly in epicardium than in endocardium, therefore creating transmural dispersion in tissue excitability [2].

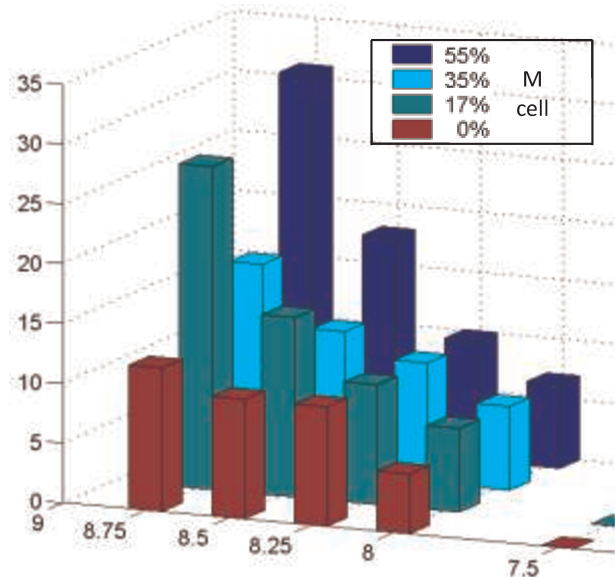


Figure 3. Barr histogram of VW distribution of reentry spiral in transmural wall in different islands of M-cell immersed onto sub-epicardial ischemia.

The spiral reentry transmural wall are difficult to study using only experimental means, because the invasive tools of cardiac tissue and the visualization for the cardiac wall makes it mandatory to obtain surgical portions of

ventricles of mammals for study wavefront movement in ischemic heterogeneous wall [6;14]. 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 [4]. This study shows how the greater epicardial sensitivity to ischemia, the heterogeneity in tissue excitability, potentiated for M cell distributions and the conduction delay combined to provide all the necessary conditions for the initiation, and terminations of transmural re-entry during regional acute ischemia [7;8;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  $[K^+]_o$  forms vulnerable windows for settling lobular rotating waves [21].

In conclusion, the model predicts that the VW for re-entry has two different stages during sub-epicardial ischemia in conjunction with the distribution of M cell into transmural wall (Antzelevitch's hypothesis) and it can be approximated by a logistic distribution.

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