SIMULATION OF ACTION POTENTIAL PROPAGATION BLOCK ON A BIDIMENSIONAL VENTRICULAR TISSUE MODEL DURING REGIONAL MYOCARDIAL ISCHAEMIA

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Abstract-**During the acute phase of myocardial ischaemia, electrophysiological alterations in ventricular cells exacerbate serious arrhythmias such as reentries. Indeed, extracellular potassium accumulation in an ischaemic zone reduces conduction velocity. Concomitantly, the activation of ATP dependent potassium current ($I_{K(ATP)}$) under ischaemic conditions provokes a reduction in action potential duration (APD), creating inhomogeneities within the tissue, which represent the main cause of unidirectional block and reentry. In this work, we investigate the patterns of activation in an isotropic ischaemic bidimensional tissue by means of computer simulations. Using the Luo-Rudy phase II model of ventricular action potential and the $I_{K(ATP)}$ formulation, we stimulated prematurely a bidimensional tissue of 5 cm^2 with a normal zone, an ischaemic zone and a border zone at different instants of time, to reproduce realistic conditions of reentry. Our results agree with experimental works and show the existence of a time interval (window of block), in which propagation is blocked in the central zone of ischaemia.**

Keywords **- Ischaemia, myocardium, reentry, unidirectional block, $I_{K(ATP)}$ current.**

I. INTRODUCTION

During the acute phase of myocardial ischaemia, important electrophysiological changes predispose the heart to the development of reentrant arrhythmias [1]. The decline in $[ATP]_i$, concomitant with the increase in free $[ADP]_i$, accounts for the activation of ATP sensitive potassium current ($I_{K(ATP)}$) [2]. The opening of these channels accelerates the repolarization of the cell, so that action potential duration (APD) is considerably reduced in the ischaemic tissue compared to APD in normal tissue [3]. Inhomogeneities in conduction velocity (CV) may also arise since potassium accumulation in ischaemic tissue responds for CV reduction [4]. Premature stimuli are susceptible to be unidirectionally blocked in an inhomogeneous tissue and thus reentry may develop [5].

In this work we study the activation patterns during myocardial ischaemia on a prematurely stimulated tissue. Mathematical formulation of the electrophysiological cellular activity in the heart ventricle (Luo and Rudy model [6]) allows this kind of study, in which every variable can be controlled in contrast to experimental studies, where the measure and control of some variables are complicated. Furthermore, computer simulations offer an important advantage, i.e. results are not sensible to the sometimes uncontrollable variability of experiments.

In a previous work [7], we simulated block of action potential (AP) propagation in a fiber composed of 100 normal cells, 100 border zone cells and 100 ischaemic cells. There was a time interval (possible vulnerable window) in which applied premature stimuli were blocked at some point in the fiber, so that the possibilities of unidirectional block and thus reentry were increased. In this work, we carry out similar simulations but on a bidimensional tissue with simulated regional ischaemia, where activation patterns are more realistic.

II. METHODOLOGY

Mathematical formulations of cellular electrophysiological activity enabled the simulation of action potential block propagation on a bidimensional tissue with regional ischaemia, under specific conditions of stimulation.

1) *Mathematical models*: We used a modified version of Luo-Rudy phase II model [6] of ventricular AP, including $I_{K(ATP)}$ formulation by Ferrero et al. [8]. The maximum current density through the Na^+-K^+ pump was increased from 1.65 to 2.61 μA/μF, which is still in the range of measured values [9], so as to achieve zero net K^+ efflux under basal normoxic conditions. This change affects AP morphology only slightly. The program was written in Fortran90 and considered also AP propagation.

2) *Electrophysilogical model of ischaemia:* The ischaemic tissue was defined as a 2D isotropic matrix of 500×500 cells. As shown in Fig.1, three different zones were distinguished. The healthy normal zone (NZ), where metabolical conditions are normoxic conditions: extracellular potassium concentration ($[K^+]_o$) of 5.4 mM, intracellular ATP and ADP concentrations ($[ATP]_i$ and $[ADP]_i$) of 6.8 mM and 15 μM respectively, and sodium and calcium channels unblocked. Along the border zone (BZ), defined as a ring 1 cm wide, metabolical conditions changed progressively until reaching ischaemic conditions, which remain stable in the central circular ischaemic zone (CZ). $[K^+]_o$ suffers a linear increase from 5.4 mM up to 12.5mM along 1 cm of tissue, while $[ATP]_i$ and $[ADP]_i$ reach the ischaemic concentration of 4.6 mM and 99 μM respectively earlier (the metabolical BZ is 1 mm). Finally, along the last 0.5 cm of the border zone, the progressive block of sodium and calcium channels begins (due to a decrease in pH) reaching a fraction of open channels in the CZ of 0.75 in both cases.

3) *Protocol of stimulation:* The stimulation protocol consisted on 2 rectangular current pulses, 2 ms in duration and amplitude 1.5 times diastolic threshold. Both were applied to the bottom edge of the tissue, i.e. to a unidimensional fiber of 500 cells. The first basic stimulus was applied after 150 ms of electrical rest to allow variable stabilization. The second stimulus was prematurely applied at different instants of time in different simulations, just following the depolarization phase of the previous AP.

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Abstract

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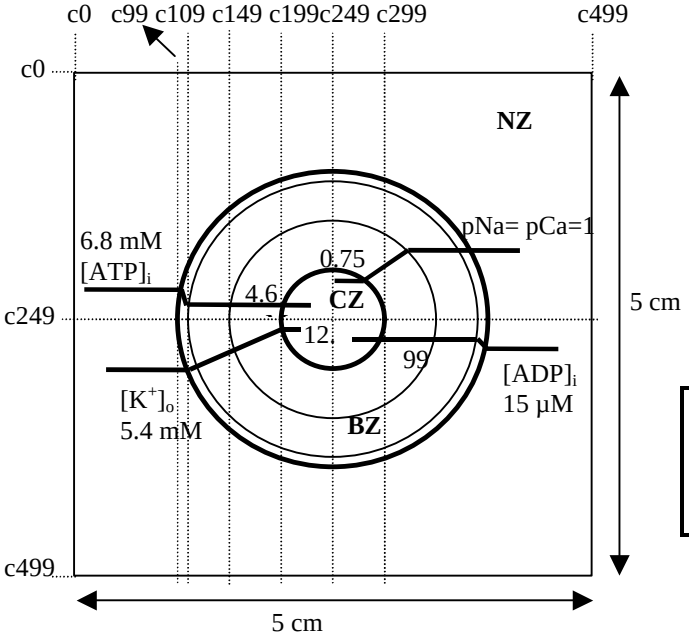

Fig. 1. Bidimensional tissue of 500×500 cells with a normal zone (NZ), a border zone (BZ) and a central ischaemia zone (CZ). Different electrophysiological conditions of intracellular ATP and ADP concentration ($[ATP]_i$ and $[ADP]_i$), extracellular potassium concentration ($[K^+]_o$ and rate of block of sodium and calcium channels (pNa and pCa) are defined.

4) *Window of block:* We defined the window of block (WB) as the time interval of the premature stimulation in which the action potential was not propagated through the whole tissue. When the instant of premature stimulation was too close to the previous basic stimulus, the action potential could not be developed, because the stimulated cells were still in refractoriness. The onset of the window was the instant from which AP propagation started. Within the window of block, this propagation stopps in a certain zone of the tissue, thus causing a block. The end of the window responds for the instant from which there was complete propagation. The window of block is shown in Fig. 2.

III. Results

The first part of our study focussed on the electrical activity of the tissue following the basic stimulus, comparing APD and CV in the different zones and looking into the activation patterns.

A. Electrical activity of the local ischaemic tissue

In the absence of electrical stimulation, we measured the resting membrane potential ($V_{m(rest)}$) in different cells of the tissue. As shown in table I, in cell (250;50) within the NZ, $V_{m(rest)}$ = -87.25 mV. This value is in the normoxic range. When measured in the BZ, the resting potential was progressively depolarized and reached the ischaemic value of –65.3 mV in the CZ.

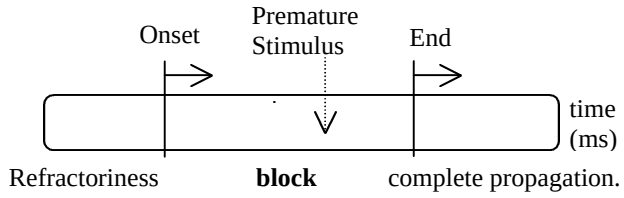

Fig. 2. Window of block in ms.

TABLE I
ELECTROPHYSIOLOGIC PARAMETERS IN THE DIFFERENT ZONES

	$V_{m(rest)}$ (mV)	APD_{90} (ms)	CV (µm/ms)
NZ Cell (250;50)	-87.25	161	500
BZ Cell (250;130)	-78.47	96.6	565
CZ Cell (250;250)	-65.3	73.25	320

Similarly, differences in APD, defined for 90% repolarization time, were observed. There was a significant APD shortening in the ischaemic zone, where APD=73.25 ms versus APD=161 ms in the normal zone, as can be estimated in Fig. 3.

The AP propagated from the bottom of the tissue towards the top with different CV. In NZ the velocity was 500µm/ms, and was reduced in the CZ to 320µm/ms. The site of faster propagation was the BZ. These different rates of CV account for the patterns of activation, shown in Fig. 4. In the proximal side of the NZ, the AP propagated exhibiting a planar wavefront. However, it became curved in the BZ and CZ where CVs were increased and released respectively.

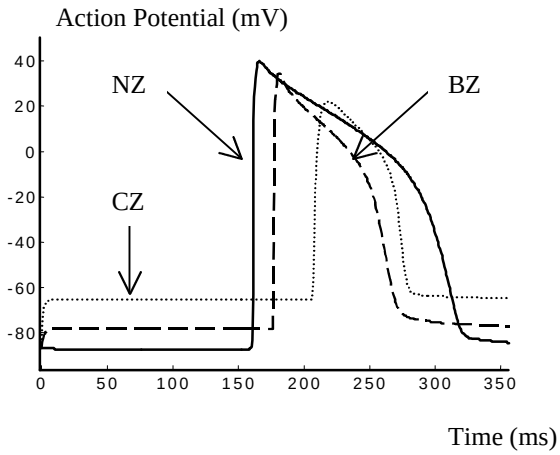

Fig. 3. Action potentials measured in different cells of the tissue. The first cell considered was cell (250;50) in the NZ, the excitation progressed and reached the BZ, action potential was then registered in cell (250;130) and finally in cell (250;250) in the CZ.

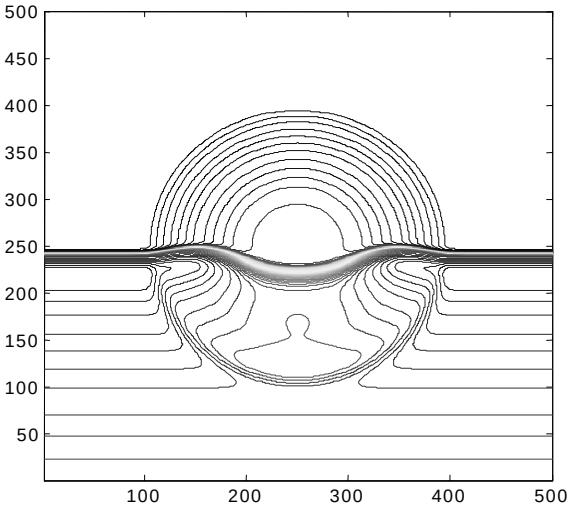

Fig. 4. Activation patterns after the first basic stimulus applied at t=150ms to the bottom fiber of 500 cells. This isopotential map was taken at t=200ms. Isopotential lines are spaced every 1.7 mV. The curved depolarizing wave is recognized by the high density of lines.

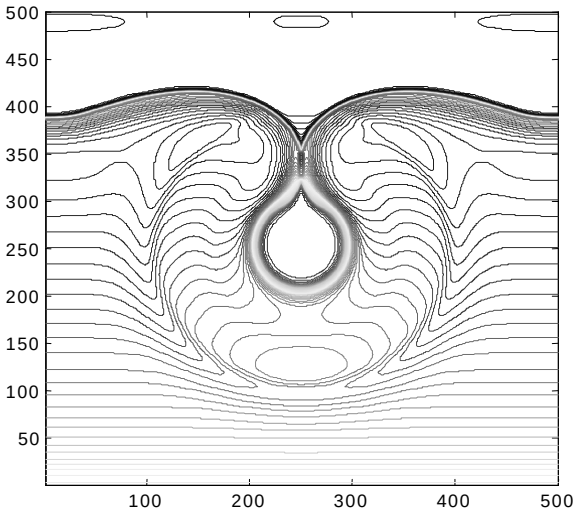

Fig. 5. Activation patterns after the premature stimulus applied at $t=t_0+170ms=320ms$ to the bottom fiber of 500 cells. This isopotential map was taken at t=412ms. Isopotential lines are spaced every 1.7 mV. The curved depolarizing wave is recognized by the high density of lines.

B. Effects of premature stimulation: the window of block

After a period of stabilization of 150 ms, during which no AP was elicited, the first basic stimulus was applied (instant t_0 = 150 ms) and propagated, as described above, through the whole tissue. Then premature stimuli (PS) were applied at the same site: the bottom fiber of 500 cells, in different simulations. If the PS was applied before instant $t_1=t_0+167ms$, AP could not develop due to refractoriness of the stimulated cells. Right at this instant of time t_1 the bottom fiber had already recovered its excitability and AP could be elicited and its propagation could progress upwards following a planar wavefront. However, when the excitation reached the BZ, propagation became faster and once it arrived to the CZ, the opposite phenomenon occurred, so that excitation surrounded the central ischaemic zone, as shown in Fig. 5. At this stage, AP block develops, since part of the CZ remained in refractoriness and could not be excited. The later the PS were applied, the smaller the zone of block was found to be, with an upper time limit. In fact, when the PS was applied later than the instant $t_2=t_0+190ms$, complete propagation was achieved. The window of block was then defined as the time interval $[t_1;t_2]=[t_1=t_0+167ms;t_2=t_0+190ms]$.

IV. Discussion

During myocardial ischaemia, important electrophysiological changes take place in the affected ventricular cells. In fact, activation of ATP dependent potassium channels provokes a reduction in APD [3]. Furthermore, extracellular potassium accumulation depolarizes the cell reducing its excitability and thus CV [4]. These changes occur only in ischaemic tissue, establishing inhomogeneities between normal and ischaemic cells, which represent the leading cause of reentry.

In this study, we simulated electrical activity of a 5 cm^2 tissue with normoxic and ischaemic cells, considering also a border zone. APD was found to be shorter inside the CZ, AP propagated slower and a depolarization was also observed. These results agreed with experimental works [3,4].

Inhomogeneities of these parameters within the tissue determined specific curved patterns of activation, after stimulating the bottom fiber of the sheet of cells. In an experimental work, Janse and Kleber [10] obtained similar patterns of activation stimulating a localy ischaemic ventricle.

When the bottom fiber was prematurely stimulated, a planar wavefront propagated in the NZ. As the excitation reached the BZ, where CV is higher, the wavefront became curved and surrounded the CZ. Two factors explain this effect. On the one hand, AP propagates slower in the ischaemic zone, and on the other hand, ischaemic cells remain still in refractoriness when the premature excitation arrives to the CZ. In fact, in this zone cells recover from refractoriness later than in BZ or NZ due to high extracellular potassium accumulation (postrepolarization refractoriness). Experimentally, during myocardial ischaemia this phenomenon of postrepolarization-refractoriness has been also demonstrated [11]. Recovery of excitability in CZ has in fact an important role to determine whether a premature stimulus is susceptible to reenter or not. In our simulations, if the excitation was applied early enough, AP propagation was blocked, whereas later stimulation could propagate through the whole sheet because the CZ had already recovered from refractoriness, when the excitation reached this zone. That is why we obtained an interval of time called the window of block.

To simulate reentry, the sheet should be larger to nest a larger CZ. In this case, when the wavefront reached the

bottom of CZ, AP would be blocked there and would propagate around this functional obstacle. However, once the excitation would reach the distal CZ, which would be already excitable, the stimulus would be able to propagate in the opposite direction and reenter. Another possibility to simulate real reentry would be taking into consideration anisotropic CV, so that in the slower direction AP would be able to propagate to the CZ already excitable, and then reenter. As we considered in our simulations, the instant of premature stimulation would also be determinant in reentry simulation, and a vulnerable window may also be defined, when reentry is susceptible to occur.

Bidimensional simulations of reentry have been carried out by several authors using different models of AP. However realistic ischaemic conditions and realistic stimulation protocol have not been taken into consideration in this kind of studies. Further investigations based on our preliminary results should allow us to analyze with a high degree of electrophysilogical detail many aspects of reentry during the acute phase of ischaemia, such as the influence of premature stimulation, pharmacological effects, and defibrillation shocks.

V. Conclusion

Computer simulations were carried out in a bidimensional ventricular tissue affected by regional ischaemia with a high degree of electrophysiological detail. The elicited AP, CV and patterns of activation were similar to experimental published results, and allow us to analyze reentry conditions.

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