Patterns of Electrical Activation in an Inhomogeneous Ischemic Sheet of Myocardial Tissue: a Simulation Study

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Abstract

Acute regional myocardial ischaemia can lead to reentrant activity under certain circumstances. Electrophysiological inhomogeneities within the tissue concomitant with premature stimuli may cause a specific type of reentry called "figure-of-eight" reentry. The aim of this work was to reproduce and analyze the patterns of electrical activation in a two-dimensional sheet of regionally-ischaemic myocardial tissue using computer modeling. Simulations were carried out using a modified version of the Luo-Rudy-II model which included a formulation of $I_{K(ATP)}$ by Ferrero et al. The simulated bidimensional tissue included a central ischaemic zone, a border zone and a normal zone. Our results show differences in APD and conduction velocity within the tissue, leading to curved patterns of activation and figure-of-eight reentries. The vulnerable window, i.e. time interval of the reentrant premature stimulus, was wider under anisotropic conditions than in an isotropic tissue.

1. Introduction

It is well known that acute regional myocardial ischaemia can favour reentrant activity [1]. Indeed, several physiological changes take place in the ischaemic tissue affecting its electrical activity. On the one hand, intracellular metabolical changes, such as the decline in $[ATP]_i$ and the increase in $[ADP]_i$, are responsible for the activation of ATP dependent potassium channels ($I_{K(ATP)}$) [2]. On the other hand, intracellular and extracellular acidosis block partially sodium and calcium channels [3], and extracellular potassium accumulation responds for membrane rest potential depolarisation and thus reduction of conduction velocity [5].

During the acute phase of regional ischaemia, the described alterations affect the ischaemic tissue, called the central ischaemic zone (CZ). In contrast, electrophysiological conditions in the normal zone (NZ) remain unchanged. There is also experimental evidence [6] of the existence of an ischaemic border zone (BZ), in which the cells gradually become ischaemic and this zone is subsequently developed separating the CZ from the NZ.

The above described electrophysiological alterations are inhomogeneous within the tissue, and favour the occurrence of reentry [5] under certain circumstances.

The aim of this work is to reproduce and analyse the patterns of electrical activation in a two-dimensional sheet of regionally-ischaemic myocardial tissue using computer modelling, so as to control every variable and to avoid the uncontrollable variability of experiments.

2. Methods

Bidimensional cellular tissues were stimulated under different conditions and their electrical activity was analysed. AP mathematical model and its propagation were necessary to carry out these simulations.

In the first instance, we considered an isotropic matrix of 650×650 cells affected by regional ischaemia. The electrophysiological conditions taken into consideration in each zone of the tissue are shown in figure 1. As shown in this scheme, 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 wide). 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.

In the second instance, we considered an anisotropic matrix of 550×550 cells affected as well by regional ischaemia. Metabolical conditions differed from those described in figure 1, in the size of the CZ. In this case, the diameter was 1 cm smaller.

In both cases, the stimulation protocol consisted on 2 rectangular current pulses, 2 ms in duration and

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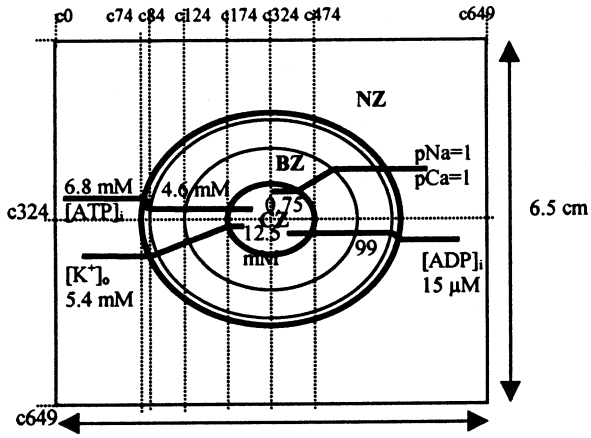

Fig. 1. Bidimensional tissue of 650×650 cells with a normal zone (NZ), a border zone (BZ) and a central ischaemia zone (CZ).

amplitude 1.5 times diastolic threshold. Both were applied to the bottom edge of the tissue, i.e. to a unidimensional fiber of 650 cells in the first set of simulations and a fiber of 550 cells in the second set of simulations. 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.

We used a modified version of Luo-Rudy phase II model [6] of ventricular AP, including $I_{K(ATP)}$ formulation by Ferrero et al. [7]. 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 [8], 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.

3. Results

The first part of our study focussed on the electrical activity of an isotropic tissue affected by regional ischaemia and prematurely stimulated.

When a basic stimulus was applied in the lower edge of the tissue, AP propagated vertically through the whole tissue. In the proximal NZ the excitation wave was planar, and the measured conduction velocity (CV) was 492.61 μm/ms. However, patterns of activation were found to be curved as they reached the BZ and the CZ. The different CV measured in these zones (respectively 534.75 μm/ms and 303.03 μm/ms) accounted for this fact.

Next premature stimuli (PS) were applied at the same site: the bottom fiber of 650 cells, in different simulations. If the PS was applied before instant t_1=317ms, 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 figure 2A. At this stage, AP block develops, since part of the CZ remained in refractoriness and could not be excitated (figure 2B). This block was then bi-directional and did not lead to reentry. Only stimulating at the instant 366 ms the block was found to be unidirectional and thus reentry developed. Finally, if the PS was applied too late, complete propagation was achieved.

The second part of our study focussed on the electrical activity of an anisotropic tissue affected by regional ischaemia and prematurely stimulated.

As described previously, a basic stimulation could propagate through the whole tissue, following a curved pattern of activation.

Propagation of premature stimuli in an isotropic tissue differed from propagation in an isotropic tissue though. As related previously, if the PS was applied too early, before instant t_1=317ms, 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. 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 figure 3A. But this time, the block was unidirectional. In fact, once the excitation reached the distal zone of CZ, cells had already recovered from refractoriness, so that AP could propagate downwards (figure 3B), reenter (figure 3C), and propagate again upwards (figure 3D). Reentry was then sustained. These observations occurred only when the PS was applied within the period of time [317 ms; 362 ms] called *vulnerable window*. Finally, if the PS was applied too late, complete propagation was achieved or bidirectional block occurred.

4. Discussion

Much attention has been paid to the electrophysiological changes that affect cardiac tissue in episodes of myocardial ischaemia. These changes alter normal cellular electrical activity in the affected region. However, in case of regional ischaemia, normal tissue remain unaffected. Inhomogeneities arise then within the tissue, favouring the occurrence of reentrant arrhythmias [5].

In this study, we stimulated prematurely and simulated electrical activity of an isotropic 6.5 cm^2 tissue and an anisotropic 5.5 cm^2 tissue, in which NZ, CZ and a BZ were considered. Our results are consistent with

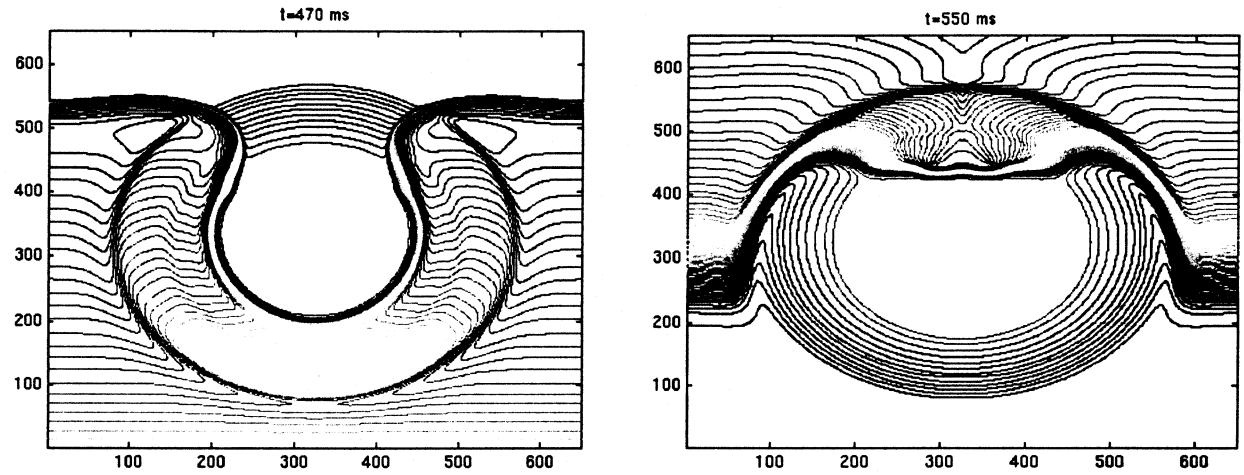

Fig. 2. Activation patterns after a premature stimulus applied at t=360ms to the bottom fiber of 650 cells. These isopotential maps were taken at t=470ms and t=550ms. Isopotential lines are spaced every 1.7 mV. The curved depolarizing wave is recognized by the high density of lines.

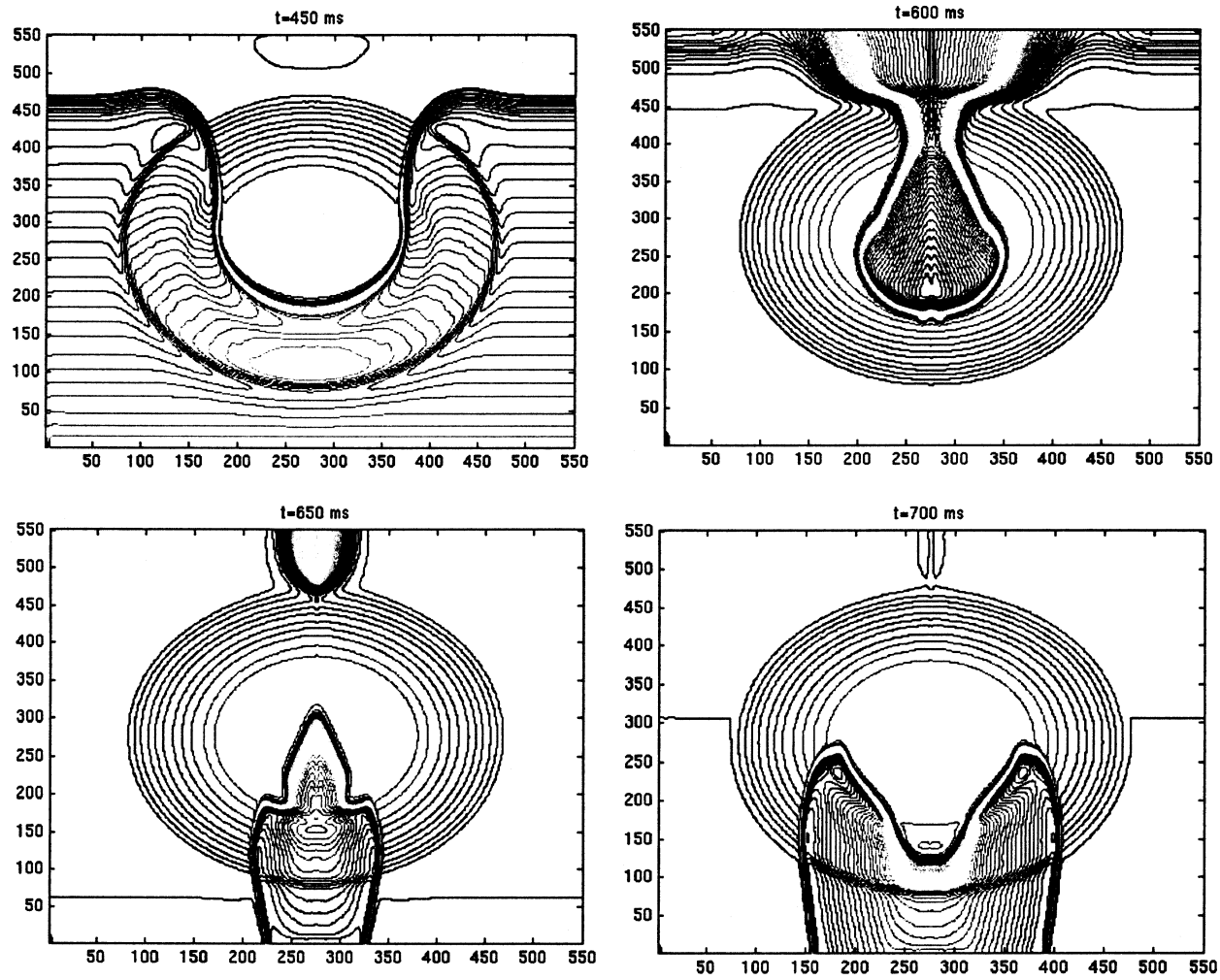

Fig. 3. Activation patterns after the premature stimulus applied at t=354 ms to the bottom fiber of 550 cells. These isopotential maps were taken at t=450, t=600, t=650 and t=700 ms respectively. Isopotential lines are spaced every 1.7 mV. The curved depolarizing wave is recognized by the high density of lines.

experimental observations showing ADP reduction and CV reduction in the ischaemic zone [9,4]. Besides, patterns of activation were curved once they reached the BZ and the CZ on account of their different electrophysiological properties. Similar results were found by Janse and Kleber [10].

Regarding the electrical activity of the isotropic tissue following a premature stimulation, we observed how a bidirectional block could hamper the complete propagation of AP. In fact, when the premature stimulation reaches the ischaemic CZ, not only CV slows down, but also ischaemic cells remain still in refractoriness. Experimental evidence support the belief that in the ischaemic tissue, where extracellular potassium accumulation provokes depolarisation of rest potential, recovers later from refractoriness than normal tissue [11]. This is the phenomenon of postrepolarisation-refractoriness. Accordingly, AP is blocked in the proximal side of CZ, and the excitation wave propagates surrounding it, without being able to reach the distal side of CZ neither. Hence, AP block is bidirectional. We did not pay attention at the unidirectional block and reentry generated after stimulating in a precise ms, because this interval of time was not significative.

In contrast, regarding anisotropic tissue, if the premature stimulus was applied within a concrete and significative interval of time called the vulnerable window, AP block was found to be unidirectional eliciting reentry. Indeed, as happened in the isotropic tissue, the AP was block in the proximal side of CZ, and the excitation wave surrounded the CZ. However, the AP could propagate through the distal side of the CZ, because the excitation reached this side later on, once it had recovered from refractoriness. Probably, the excitation of the distal site came transversally, and thus later due to the slow transversal CV. The AP could then propagate downwards through the whole CZ and reenter. Our results show the importance of anisotropy in generation of reentries.

Even if there are many experimental studies focussed on reentry and its generation, computer simulations and thus mathematical models of cellular electrical activity provide an alternative tool to make further research in this field. In fact they allow to analyse with a high degree of electrophysiological detail many aspects of reentry such as the profound study of its causes, the influence of premature stimulation, pharmacological effects, defibrillations shocks, etc. Only computing limitations restrain the use of this tool. In fact the more realistic the models are, the bigger memories and computing time are needed.

5. Conclusions

Computer simulations of the electrical activity of a bidimensional ventricular tissue affected by regional ischaemia were monitored. Unidirectional conduction block and reentries were analysed and anisotropy was found to be a determinant property to generate reentry.

Acknowledgements

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References

[1] Rensma PL, Allessie MA, Lammers WJEP, Bonke FIM, Schalij MJ. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ. Res. 1988, vol 62, pp. 395-410.

[2] Kakei M, Noma A, Shibasaki T. Properties of adenosine-triphosphate-regulated potassium channels in guinea-pig ventricular cells, J. Physiol 1985, vol 363, pp. 441-462.

[3] Kagiyama Y, Hill JL, Gettes LS. Interaction of acidosis and increased extracellular potassium on action potential characteristics and conduction. Circ. Res. 1982, vol 51, pp. 614-623.

[4] Rosen MR, Janse MJ, Wit AL. Cardiac electrophysiology. Ed. Futura Publishing Co., Mt. Kisko, New York, 1990.

[5] Janse MJ, Van Capelle JL, Morsink H, Kleber AG, Wilms-Schopman F. Flow of injury current and patterns of excitation during early ventricular arrhythmias in acute regional myocardial ischaemia in isolated porcine and canine hearts, Circ. Res, 1980, vol 47, pp. 151-165.

[6] Luo CH, Rudy Y, A dynamic model of the cardiac ventricular action potential. 1. Simulations of ionic currents and concentration changes. Circ. Res.1994, vol 74, pp. 71-1096.

[7] Ferrero (Jr) JM, Saiz J, Ferrero JM, Thakor N. Simulation of action potentials from metabolically impaired cardiac myocytes . Role of ATP-sensitive K^+ current. Circ. Res, 1996, vol 79, pp. 208-221.

[8] Mogul DJ, Singer DH, Ten Eick RE. Dependence of Na-K pump current on internal Na in mammalian cardiac myocytes. Am. J. Physiol, 1990, vol 259, pp. H488-H96.

[9] Nakaya H, Takeda Y, Tohse N, Kanno M. Effects of ATP-sensitive K^+ blockers on the action potential shortening in hypoxic and ischaemic myocardium, Br J Pharmacol, 1991, vol 103, pp. 1019-1026.

[10] Janse MJ, Kleber AG. Electrophysiological changes and ventricular arrhythmias in the early phase of regional myocardial ischaemia. Circ. Res, 1981, vol 49, pp. 1069.

[11] Downar E, Janse MJ, Durrer D. The effect of "ischaemic" blood on transmembrane potentials of normal porcine ventricular myocardium. Circulation, 1977, vol 55, pp. 455-462.

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