THE EFFECTS OF ISCHEMIA ON THE ECTOPIC ACTIVITY INDUCED BY EADs. COMPUTER SIMULATION.

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Abstract – **Computer simulations have been used to study the conditions required for the development of EADs in the ventricular myocardium, and their propagation to regions with acute myocardial ischemia, thus causing ectopic activity. A modified version of the Ludo-Rudy phase II model of the cardiac ventricular action potential was used, with the formulation of the ATP-sensitive K^+ current by Ferrero et al. being adopted. The structure of ventricular cells is considered to consist on: an EAD zone, induced by increasing I_{Ca} currents and by decreasing I_k currents; a border zone which separates the EAD zone from the ischemic zone; another border zone, similar to the previous one, which separates the ischemic zone from the last zone (normal cells). The different characteristics of the border zone influencing the development of ectopic activity (e.g. size of the border zone, $[K^+]_o$ values, etc) are also studied. The results show that ectopic activity depends both on EAD conditions and on the parameters of the border and ischemic zones. In larger border zones (20 cells), ectopic activity only occurs under high EAD conditions (a 100% increase in I_{Ca} and a 60% decrease in I_k). If the border zone is half as large (10 cells) ectopic activity can occur with an 80% increase in I_{Ca}, and in ischemic zones even with lower $[K^+]_o$ values. This work shows that in a myocardial region with acute ischemia the ectopic activity can be induced by the development of EADs in a nearby zone and can propagate to normal zones.**

I. INTRODUCTION

Early afterdepolarizations (EADs) are membrane potential depolarizations that occur in phase II or phase III of the repolarization process and that are favoured by low stimulation frequencies [1]. EADs can cause delay in repolarization or generate a secondary depolarization of the membrane potential, which may result in induced action potential (AP). EAD development is generally associated with a critical extension of the AP repolarization phase due to the decrease of the outward net currents. Such decrease in the repolarizing current can be provoked by increasing one or more inward currents, by decreasing one or more outward currents, or by the combination of both [2]. Different mechanism can lead to the generation of EADs; such as the decrease of the K currents or the increase of the Ca currents. Other mechanisms are the injection of the depolarization current and hypokalemia. In multicellular preparations, EADs can be developed by the electrotonic interaction between cellular zones with different action potential duration [3].

On the other hand, acute ischemia causes important changes in the electrical activity of cardiac tissue. Ischemia causes the reduction of the membrane resting potential, of the action potential duration (APD) and of the conduction velocity, in addition to other electrophysiological effects [4]. These changes are responsible for the arrhythmias caused during acute ischemia. The effects of ischemia after coronary artery occlusion are not homogeneous in space. When ischemia develops, the cells directly affected by the lack of blood flow lose K+ and the ATP-sensitive K current is somehow activated, generating an ischemic central zone (CZ). While the cells far from the CZ (normal zone or NZ) keep their electrophysiological properties normal, between NZ and CZ a border zone (BZ) appears, in which $[K^+]_o$ gradients occur. In addition, within BZ and close to NZ a metabolical border zone (MBZ) appears in which pO_2 gradients are present; this causes a gradual activation of the $I_{K(ATP)}$ in a small area. This situation generates spatial differences in the configuration of the action potential affecting the APD which favours the generation and propagation of EAD induced ectopic APs.

In this work, we have used computer simulations to study the electrophysiological behaviour of a regionally ischemic tissue with an adjacent EAD-developing zone, and the conditions under which the EADs generated in the latter are able to induce ectopic beats which result in reentry.

II. METHODOLOGY

A modified version of phase II Luo-Rudy model of the cardiac action potential was used to represent the electrical activity of the cardiac cells [5-6]. $I_{K(ATP)}$ currents, as formulated by Ferrero et al, was included in the basic Luo-Rudy model in order to simulate Hypoxia in the BZ and CZ [7]. The final model represents the basic features of AP and the electrical currents through the sarcolemma with a great degree of electrophysiological detail.

The simulation was carried out with a sample of five one-dimensional segments of myocardial cells. Each cell was 100μm long and was electrically connected to each other by gap-junctional resistances of 2 Ωcm^2. Electrical resistivity of the intracellular space was also kept within its normal range (200Ωcm).

The first segment consists of 100 cells (#0 to #99); EADs were induced by increasing I_{Ca} values within a range between 60 to 100% and by decreasing I_K values within a range of about 20 to 60%.

The second segment is the BZ; it consisted on a variable number of cells (#100 to 99+x), where x is a variable that defines the length of the BZ. In this zone, $[K^+]_o$ increased

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from its normal value (5.4mM) to ischemic values in the range of 10.5mM to 13.5mM (the effect of this parameter was also studied in this paper). A metabolical border zone 1mm in length was situated within the electrophysiological BZ adjacent to the normal zone. In this space, formed by only 10 cells (#100 to #109), intracellular $[ATP]_i$ and $[ADP]_i$ values were decreased and increased, respectively, from their normal to their ischemic values.

The third segment corresponds to the ischemic central zone (CZ) and was made up of 100 cells (#100+x to #199+x); it was simulated with the following concentrations: $[K^+]_o$ = 10.5 mM to 13.5 mM (this value is variable); $[ATP]_i$ = 4.6mM; and $[ADP]_i$ = 100µM.

The fourth segment is another BZ similar to the zone mentioned in the second segment; it separates the ischemic zone from the normal zone (NZ). In this zone, the MBZ was situated within the BZ, adjacent to the NZ. The number of cells was x (#200+x to #199+2x). Its MBZ also consisted of 10 cells **(#**190+2x to #199+2x).

The fifth and last of the segments represents normal tissue and comprised 100 cells (#200+2x to #299+2x). The ionic and metabolical concentrations were kept constant and within their normal ranges ($[K^+]_o$ =5.4mM, $[ATP]_i$ = 10^9 mM y $[ADP]_i$ = 0µM).

Figure 1 represents the spatial distribution of $[K^+]_o$, $[ATP]_i$ and $[ADP]_i$, described above.

In order to reach the steady-state conditions of the ionic concentrations and of all time/stress-dependent variables normal physiological conditions were fixed for the first segment of the model and a frequency of 0.5Hz (10 pulses) was simulated during 20" for each combination of the x (BZ size) and $[K^+]_o$ values analysed. Then I_{Ca} and I_K values were modified, and one only pulse 1ms in duration and an amplitude 1.2 times the diastolic triggering threshold value was applied; subsequently, the action potential was recorded.

The cable equation was solved using a central difference scheme in space and the Crank-Nicholson method in time with a space interval of Δx=100µm. The modified Euler method with a time increment of Δx=8µs was used to solve the non-linear system of differential equations which describe ionic current kinetics. Von Neumann's boundary conditions were employed. The model was programmed in C++ language and implemented in a Convex SPP 1000/XA Exemplar workstation.

III. RESULTS AND DISCUSION

In all the simulations, stimuli were applied to cell #0. Once the steady state was reached (simulation for 20 seconds at a frequency of 0.5Hz), I_{Ca} and I_K values were modified in the first segment in order to simulate EAD conditions, and the segment was stimulated with only one pulse under EAD conditions.

Figure 2 shows the action potentials elicited when the last stimulation pulse was applied to the segment under EAD conditions (cells #0 to #99) for different characteristics of the border zones, such as different lengths (x) and different final $[K^+]_o$ values. In the figure the EADs were induced by increasing I_{Ca} in about 100% and by decreasing I_K in about 60%.

For the case of 30 cells in the border zones (x=30), the EADs that occurred in the first segment did not induce ectopic activity in the ischemic zone nor in the normal zone for any of the $[K^+]_o$ values analysed.

For x=20 the ectopic activity was induced in the ischemic zone as well as in the normal zone only when $[K^+]_o$ = 13.5mM. In the other cases studied ($[K^+]_o$ = 12mM and $[K^+]_o$ = 10.5mM), action potential propagated in the first segment (EADs) but ectopic activity was not elicited in the other segments.

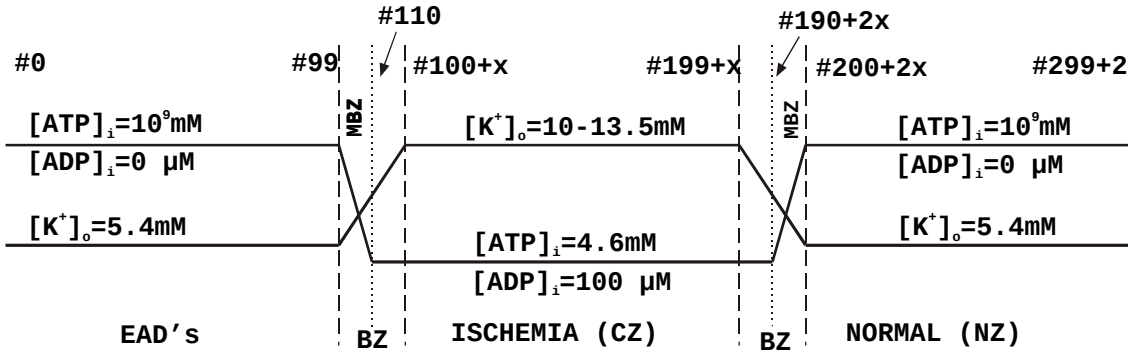

Fig. 1. Schematic representation of the myocardial tissue. The figure shows the spatial distribution of ion and metabolite concentrations.

For x=10 the ectopic activity was induced for all the $[K^+]_o$ values analysed ($[K^+]_o$ = 13.5mM, $[K^+]_o$ = 12 mM and $[K^+]_o$ = 10.5mM), and under the EAD conditions described above (100% increase in I_{Ca} and 60% decrease in I_K). Ectopic activity was also elicited under other EAD conditions (80% increase in I_{Ca} and 60% decrease in I_K) in similar border zones (x=10)

It was also observed that when etopic activity is present, APD values in cell #0 are higher than when no etopic activity occurs; the APD value is about 250 ms higher in the first case than in the second, in the specimens analysed. Coupling interval (CI) was measured in cells #149 and #249 in the cases in which a second ectopic beat occurs, obtaining values of about 350 ms in both cases. CI was related to APD

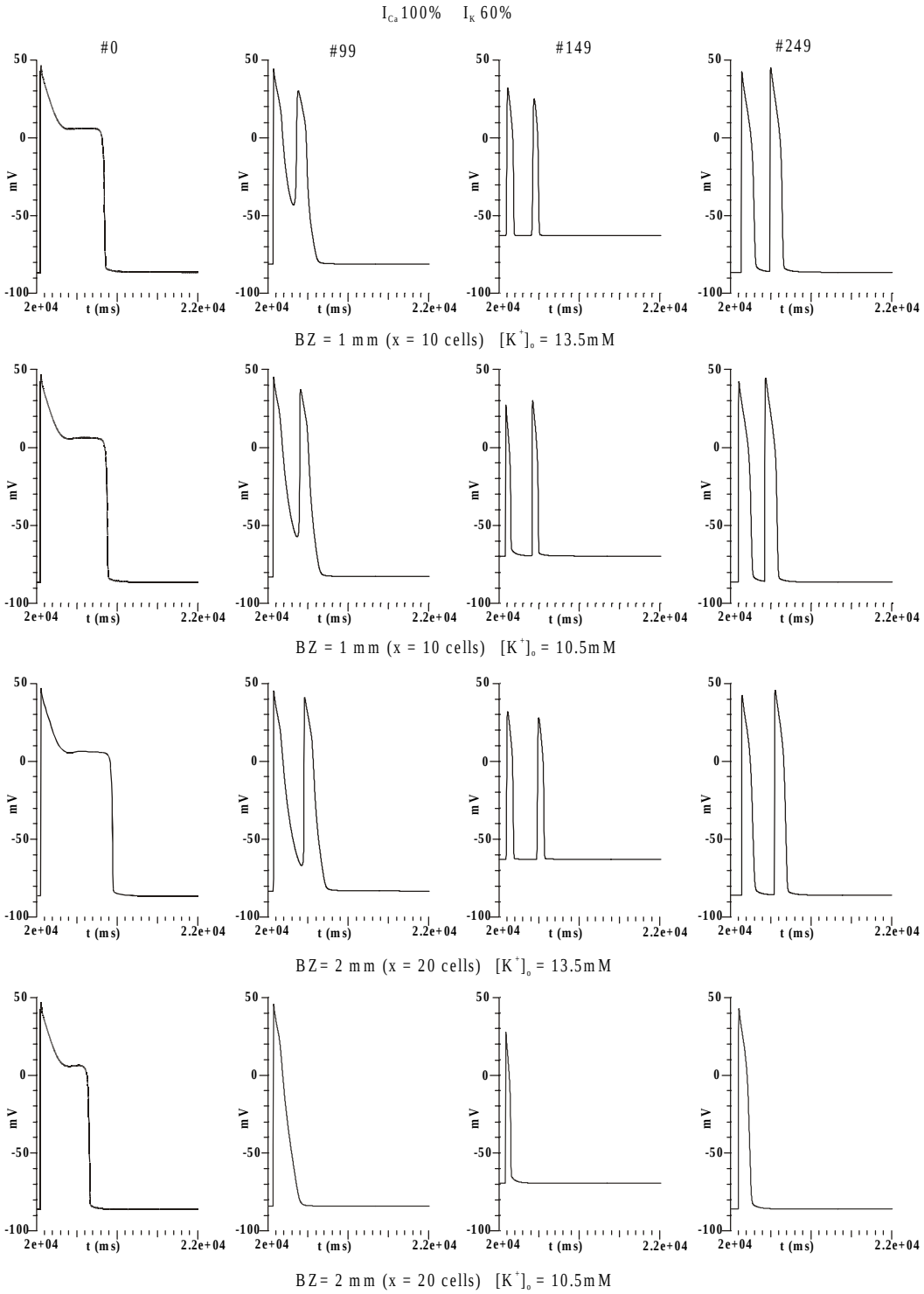

Fig. 2. Action potentials (AP) under different conditions.

and in most cases, the higher the APD the higher the IC.

The results show that the electronic interactions between a zone of ventricular tissue where EADs have been induced and an ischemic zone may cause the propagation of EADs as ectopic beats. In previous work the influence of electrical coupling on the propagation of EAD as ectopic activity in ventricular tissue has been suggested [8]. For a border zone length of 20 cells ectopic beats only occur under acute ischemic conditions ($[K^+]_o$ = 13.5mM). In smaller border zones, ischemia conditions can be less depressed (shorter response time between the appearance of the ischemic episode and the moment analysed).

IV. Conclusion

Our results suggest that when a zone of ventricular myocardium where EAD's can be elicited is coupled to a normal tissue through an inhomogeneous ischemic zone, EAD's can be propagated to normal ventriculum as ectopic activity. The results also shows the influence of the size of the border zone and the extracellular potassium concentration on the ectopic beat generation.

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