Simulation of Reentry Induced by Early Afterdepolarizations During Acute Myocardial Ischemia

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Abstract

Computer simulations were used to study the conditions which lead to the appearance of ectopic foci and to their propagation as reentrant activity in partially ischemic tissue. To simulate action potentials, we used a modified version of the Luo-Rudy-II model completed with the formulation of the ATP-sensitive potassium current [IK (ATP)] by Ferrero et al. The tissue was simulated as a ring-shaped structure comprising four different regions: EADs, normal, ischemic and border zones. Our results show that, when the length of each BZ is 2mm, [K]o is 13.5 mmol/L and the length of the NZ is higher than 26mm (260 cells), (a) ectopic beats appear in the EAD region and (b) they propagate along the tissue causing reentry regardless of the length of the NZ. In conclusion, our theoretical study shows that the co-existence of EAD condictions zone and regional ischemia could set the stage for the appearance of ectopic foci and reentry.

1. Introduction

Early afterdepolarizations (EADs) are oscillations of membrane potential which take place during the repolarization of the cardiac action potential [1]. Different mechanisms may lead to the generation of EADs, such as: pharmacological interventions, which act by reducing potassium currents which contribute to the repolarization, by increasing the calcium current, or by delaying the inactivation of the sodium current. Other mechanisms are the injection of depolarizing current and hypokalemia. In multicellular preparations, another possible mechanism of generation of EADs is the electrotonic interaction between areas with different action potential durations[2].

The appearance of EADs is usually associated with a critical prolongation of the AP repolarization stage and, in some situations, EADs lead to a secondary depolarization of the membrane potential which may to induce triggered action potential (AP) [3,4].

On the other hand, acute ischemia causes important changes in the electrical activity of the tissue. Ischemia causes a decrease of the action potential duration (APD), of the membrane restitution potential, as well as changes in conduction velocity, in addition to other electrophysiological properties [5]. These changes, during the acute phase of ischemia are usually responsible for arrhythmias. The effect of ischemia after the occlusion of a coronary artery are not homogeneous in space. When ischemia develops, the cells directly affected by the loss of blood supply lose K^+ and the ATP-sensitive potassium current [$I_{K(ATP)}$] is slightly activated, resulting in a central ischemic zone (CZ). While cells far from the CZ (normal zone or NZ) keep their normal electrophysiological properties, a border zone (BZ) develops between the NZ and the CZ, where a gradient of $[K^+]_o$ is produced. A metabolical border zone (MBZ) also develops within the BZ and next to the NZ where a gradient of pO_2 is created, which causes, within a small space, a gradual activation of the $I_{K(ATP)}$. This scenario provokes spatial differences in the configuration of the action potential affecting the APD and facilitating reentry. The concept of reentry implies that the propagated AP does not disappear after the complete activation of the heart, on the contrary, it persists to re-excite the heart or one of its zones after the refractory period. In our case, the connection of a EAD zone with an ischemic zone contributes to the generation of ectopic foci in the EAD zone, and their propagation throughout the ischemic zone (where the speed of conduction is slower) and in the normal zone, reaching again the EAD zone after the refractory period and, therefore exciting again such cells and repeating the process. The aim of this work is to study the conditions under which this type of reentry occurs.

2. Methods

We have used phase II model of the cardiac action potential by Luo-Rudy to represent the electrical activity of the cardiac cells [6-7], in which we included the $I_{K(ATP)}$ current formulated by Ferrero et al. in order to simulate hypoxia in the BZ and CZ [8]. This model represents with great electrophysiological detail the basic characteristics of the AP and the electrical currents through the sarcolemma.

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Computers in Cardiology 2001;28:357-360.

The simulation was performed in a unidimensional model of myocardial cells consisting of five segments which linked together conforming a ring-shaped structure. Each cell has a length of 100μm and is electrically connected to its neighbors with a gap-junctional resistance of 2 Ωcm^2. The resistivity in the intracellular space was kept within its normal range (200 Ωcm).

In the first 100 cells form the first segment (#0 to #99), EADs are induced by increasing the I_{Ca} within a range from 60% to 100% and decreasing the I_K ranging from 20% to 60%.

The second segment is the BZ, and it consists of 20 cells (#100 to #119). In this zone $[K^+]_o$ is increased from its normal value (5.4mM) to its ischemic value (13.5 mM). Within the border zone, a metabolic border zone (MBZ) was simulated along 1 mm located next to the EADs zone; that is, it consists of 10 cells (#100 to #109). In the MBZ, $[ATP]_i$ is decreased and $[ADP]_i$ in increased from their normal to their ischemic values.

The third segment corresponds to the central ischemic zone (CZ) and consists of 100 cells (#120 to #219), it is simulated with the following concentrations $[K^+]_o$ = 13.5mM, $[ATP]_i$ = 4.6mM and $[ADP]_i$ = 100μM.

The fourth segment is another BZ similar to the one described in the second segment. In this zone, the MBZ is located within the BZ next to the NZ. The MBZ of this segment consists also on 10 cells.

The fifth and last segment represents normal tissue and consists on a variable number of cells (#240 to #240+x), in which x is a variable to study in order to see the influence of the size of the normal zone on the generation of reentries. The ionic and metabolic concentrations remain constant and within their normal ranges ($[K^+]_o$ = 5.4mM, $[ATP]_i$ = 10 mM and $[ADP]_i$ = 0μM.

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

In order to reach the stationary conditions of the ionic concentrations and of all the time-dependent and voltage variables, some normal physiological conditions were set in the first segment of the model and it was stimulated during 20 s at a frequency of 0.5Hz (10 pulses) for each one of the values of x studied (size of the NZ). Then, the I_{Ca} and the I_K were modified and a single current pulse was applied during 1ms and with an amplitude of 1.2 times the diastolic threshold.

The cable equation was solved by using central differences in space and the Crank-Nicholson method in time with a spatial increment of Δx=100μm. Euler modified method with a time increment of Δt=8μs was used to solve the non-linear system of differential equations which describes the kinetics of the ionic currents. The model was programmed in C++, and implemented in a workstation Convex SPP1000/XA Exemplar.

3. Results and discussion

The stimuli were applied to cell #0 in all the simulations. After the stationary state was reached (stimulation for 20 seconds at a frequency of 0.5Hz), the I_{Ca} and the I_K were modified in the first segment to simulate the EAD's conditions and the segment was stimulated under EAD conditions with only one pulse.

In the first part of our study, the effect of the different parameters on the appearance of ectopic foci were observed. Among the parameters studied are the length of the border zone and the $[K^+]_o$ level in the ischemic zone. After obtaining the results of such study, we proceeded to the second stage, where we used the values obtained in the previous stage, regarding the size of the border zone and $[K^+]_o$ which generated ectopic foci (which were: size of BZ = 20 cells and $[K^+]_o$ = 13.5mM). In this second stage we modified the size of the NZ from a value of 260 cells to a value of 960 cells.

The results show that, in all the cases studied, an AP is generated in the EAD zone, which propagates to the ischemic zone and to the normal zone reentering again

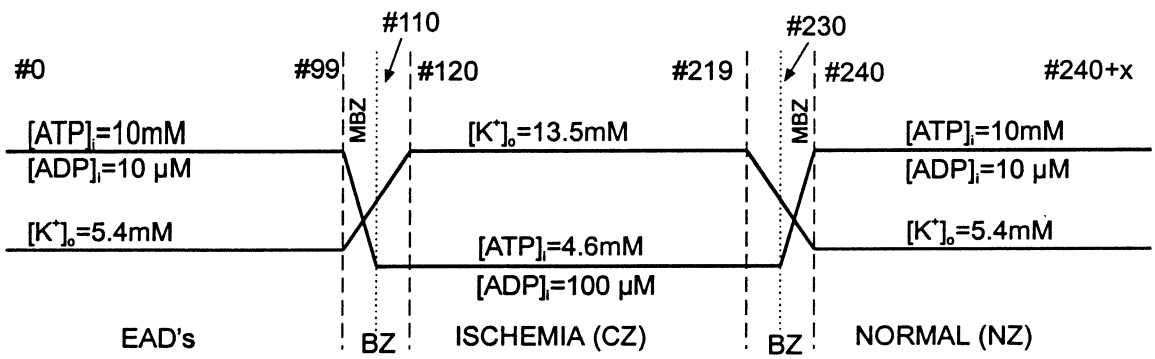

Figure 1. Diagram of the simulated tissue.It shows the spatial distribution of the ion and metabolite concentrations

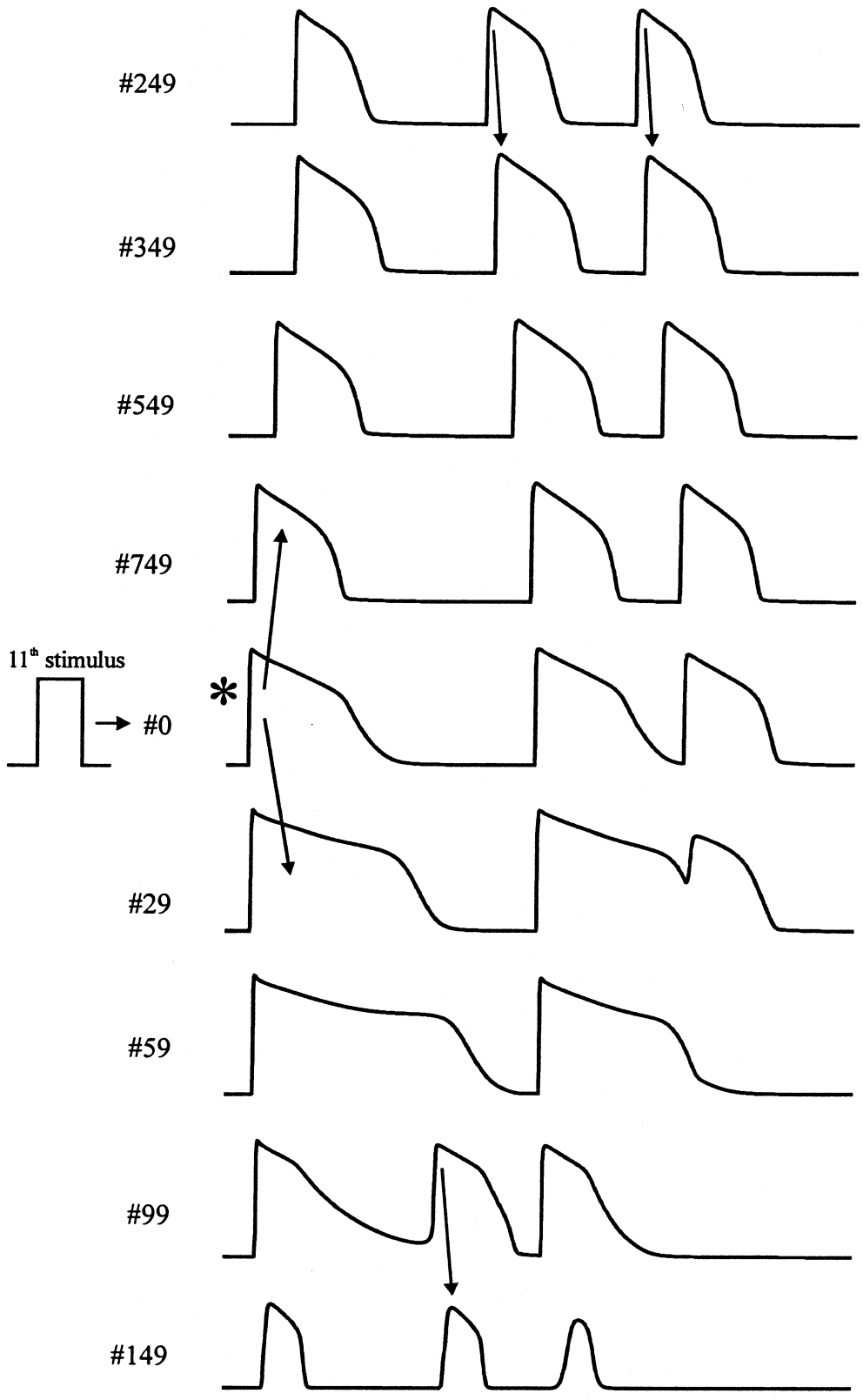

Figure 2.- Action potentials in different cells for case of a NZ = 560 cells.
* Last stimulus, pulse 11.

the EAD zone. It was also observed that for a number of cells in the NZ lower than 560, this AP that reenters the EAD zone and reaches the ischemic zone is not capable of propagating throughout such zone, since the cells are in their refractory period and are not excited by the reentering AP. On the other hand, for a number of cells in the NZ higher than 560, such AP propagates throughout the ischemic zone and the normal zone generating a second reentry to the EAD zone. This second reentry does not reach the ischemic zone because in the EAD zone, the AP is lengthened and when it reaches this second reentry, the AP is still active from the first reentry, therefore the excitation of such cells cannot be produced resulting in a cessation of the propagation of the second reentry.

Figure 2 shows the induced action potentials when the last stimulation pulse was applied to the segment under EAD conditions (cells #0 to #99). This simulation corresponds to a NZ comprising 560 cells. In the figure, the EAD's were induced by increasing I_{Ca} by 100% and decreasing the I_k by 60%.

The coupling interval (CI) in the AP recorded in cell #0 was measured, observing that it depends on the length of the NZ and that the CI increases when the size of the NZ is increased. The results are shown in the following table.

No. cells NZ	CI1 (ms)	CI2 (ms)
260	549	
360	572	
460	593	
560	612	319
760	651	316
960	693	335

Table 1. CIs according to the size of the NZ

4. Conclusions

Our theorical study shows that the co-existence of an EAD-conditions zone and regional ischemia can set the stage for the appearance of ectopic foci and reentry.

Acknowledgements

We would like to thank the Foreign Language Co-ordination Office at the Polytechnic University of Valencia for their help in translating this paper.

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