Effects of Acute Ischemia on the Restitution Curves of Myocardial Tissue: A Simulation Study

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Abstract

The Electrical Restitution Curve (ERC) may play an important role in the generation and maintenance of Ventricular fibrillation (VF). As VF usually appears in ischemic hearts, we have studied the changes exerted by acute ischemia in ERCs using computer simulations.

Our results show that the main effects of ischemia on the ERC are that (a) it shifts the ERC towards lower action potential durations (APDs) and (b) it significantly reduces the slope of the ERC. These findings are in accordance with experimental observations.

When analyzing ionic currents, it became clear that, as expected, the slow component of the delayed K current (I_{Ks}) was responsible for the slope of the ERC in normal conditions. However, an increased Ca inward current (I_{CaL}) provoked by the altered $[Ca^{2+}]_i$ dynamics accounted for the flattening of the ERC in ischemia.

1. Introduction

Ventricular tachycardia (VT) and ventricular fibrillation (VF) are potentially mortal arrhythmias frequently caused by reentrant electrical activity in heart ventricles. These arrhythmic processes usually arise during myocardial ischemia [1], when important electrophysiological cellular changes take place. Indeed, acidosis, hyperkalemia and hypoxia observed during ischemic episodes affect action potential (AP) morphology and propagation. Among other changes induced by ischemia, experimental studies show that a reduction of the action potential duration (APD) is exerted and the Electrical restitution curves (ERCs) of cardiac cells (variation of the APD with the previous diastolic interval (DI)) is also modified [2]. Much attention has been paid to ERCs as it is known that it may play an essential role in arrhythmogenesis [2].

However, a recent controversy exists regarding the pro or antifibrillatory effect of a high slope in the ERC [2]. On the one hand, electrical alternans, reliable precursor of ventricular fibrillation (VF)[2], are known to be enhanced by a ERC slope higher than one. On the other hand, in some experimental studies of ischemic episodes related to arrhythmic processes, a flattening in ERC has been observed [2].

As VF normally appears in ischemic hearts rather than normal hearts, in this paper, we have simulated ERCs during 5 and 10 minutes after the onset of ischemia, besides during normoxia, in order to study not only the morphology of these curves in acute ischemia but also to investigate the ionic mechanisms responsible for its behavior.

2. Methods

In order to simulate cardiac action potentials a modified version of the 2000 Luo-Rudy model [3 (without its $I_{K(Na)}$ formulation)] was chosen. Simulations were carried out in a homogeneous 400 cell 1D strand. Excitatory current was applied in cell number 200, while APD_{90} was measured in cell number 299.

Acute ischemia was reproduced by means of its three main components. For this purpose, those parameters affected were set according to those experimentally observed at different instants after the onset of ischemia, as shown in Figure 1. Firstly, hypoxia was considered by partially activating the ATP-sensitive K^+ current ($I_{K(ATP)}$), using the mathematical formulation of Ferrero Jr. et al. [4] and intracellular values of ATP and ADP ($[ATP]_i$ and $[ADP]_i$) were set to values in the range of 6.8-4.6 mmol/L and 15-199 µmol/L respectively [5,4]. Secondly, hyperkalemia was simulated by elevating extracellular K^+ concentration ($[K^+]_o$). In particular, $[K^+]_o$ was set to a value in the range 5.4-12.5 mmol/L [5,6]. Finally, acidosis was taken into account by its effect on the Na^+ and Ca^{2+} current [7,8]. Hence, the fast inward Na^+ current (I_{Na}) and the Ca^{2+} current through the L-type channels ($I_{Ca(L)}$) were affected by a factor f_{pH} comprised between 1.0 and 0.75 [7,8].

A dynamic protocol was used to obtain the ERCs. Thus, each simulation was carried out with a constant basic cycle length (BCL). The protocol of stimulation in each simulation consisted on a train of 10 driven
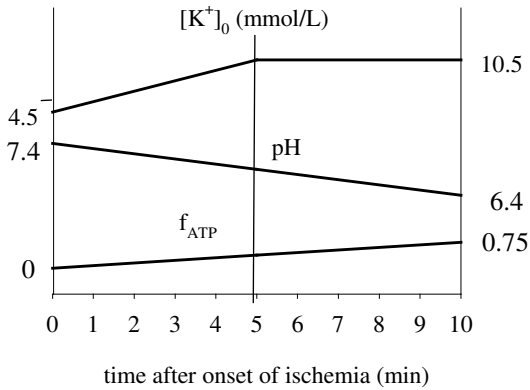
Figure 1. Time course of relevant parameters after the onset of myocardial ischemia

Figure 2. ERCs during normoxia, 5 and 10 minutes after the onset of ischemia.

rectangular pulses of 2ms in duration and twice the diastolic threshold in amplitude.

APD_{90} was measured at 90% of repolarization in the last action potential elicited. Several simulations were carried out in order to represent the ERC corresponding to those situations of normoxia, 5 minutes of ischemia and 10 minutes of ischemia. For each curve, the first DI considered was the shortest that did not lead to alternans.

3.   Results

As shown in Figure 2, during normoxia APD remains almost constant at high DIs, though for shorter DIs APD reduction presents a small notch at DI of 46 ms (BCL = 150 ms). It also becomes clear that the slope tends to increase for shorter DIs, but never reaches the unity, the highest slope being 0.555 at a DI of 27 ms (BCL = 120 ms, which is supported by many studies [2,9,10]. This notch [2] and the increase of slope at small DIs [2,11] are also in accordance with experimental results.

Regarding ischemia, it is important to notice several phenomena. On the one hand, the more ischemic the tissue is, the shorter the APD is [2], as expected. On the other hand, ischemia flattens the ERC [2] reaching even negative slopes when ischemia is completely developed, (10 minutes after its onset). At the stage of 5 minutes of ischemia, a maximum slope of 0.5 at a DI of 85 ms (BCL = 160 ms) is observed, while after 10 minutes this maximum is significantly lower (0.16) at DI of 97.4 ms (BCL = 160 ms). For both cases, the maximum slope never reaches unity, which is also in accordance with experimental results [2,10].

To investigate the ionic mechanisms explaining the flatter ERC in ischemia, different ionic currents have been compared (Figure 3). Firstly, we have studied normoxia at high and at low DIs in order to investigate the mechanisms responsible for the shortening of the AP when the rate pace increases. Secondly, acute ischemia
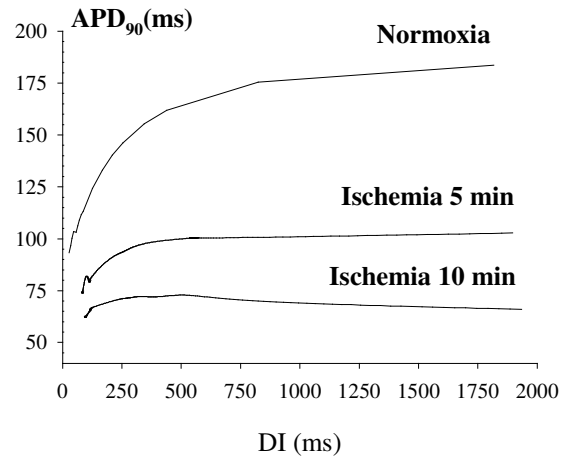
has been considered to detect the causes of its different behavior.

In analyzing the positive slope in normoxia, we have compared those currents that significantly influence APD. For this purpose DIs of 850 ms and 210 ms (which corresponds to BCLs of 1000 ms and 350 ms respectively) have been considered. It is known that fast sodium current (I_{Na}) [11], L-type calcium current (I_{CaL}) [11], the slow component of the delayed potassium current (I_{Ks}) [12] and the fast component of the delayed potassium current (I_{Kr}) [12] may play a relevant role. I_{Na} has been discarded as it just plays a significant role at very short DIs [11]. Panels A through D of Figure 3 show the time course of both APs and currents in normoxia for the previously selected DIs. As depicted in Figure3A, both APs follow a similar time course until 15 ms after its onset. As the time course of I_{Kr} in both cases starts to differ after this instant, this current seems not to be a cause of the discrepancies between both AP. Thus, much attention is going to be paid to I_{CaL} and I_{Ks} as they are the only ones that show differences between both DIs prior to 15 ms. Regarding I_{CaL}, but for the fast peak, this current presents a higher absolute value within the first 15 ms at 210 ms, being 0.7 µA/µF the difference at 5 ms. This increase should provoke a longer APD at a DI of 210 ms. On the other hand, I_{Ks} at a DI of 210 ms is much higher than I_{Ks} at DI of 825 ms throughout the first 15 ms, specifically at 5 ms the difference is 0.78µA/µF. This last increase is large enough to counteract the effect of I_{CaL} and to shorten the APD. Therefore, we conclude that I_K is responsible for APD shortening in normoxia for short DIs, which is in accordance with other studies [12].

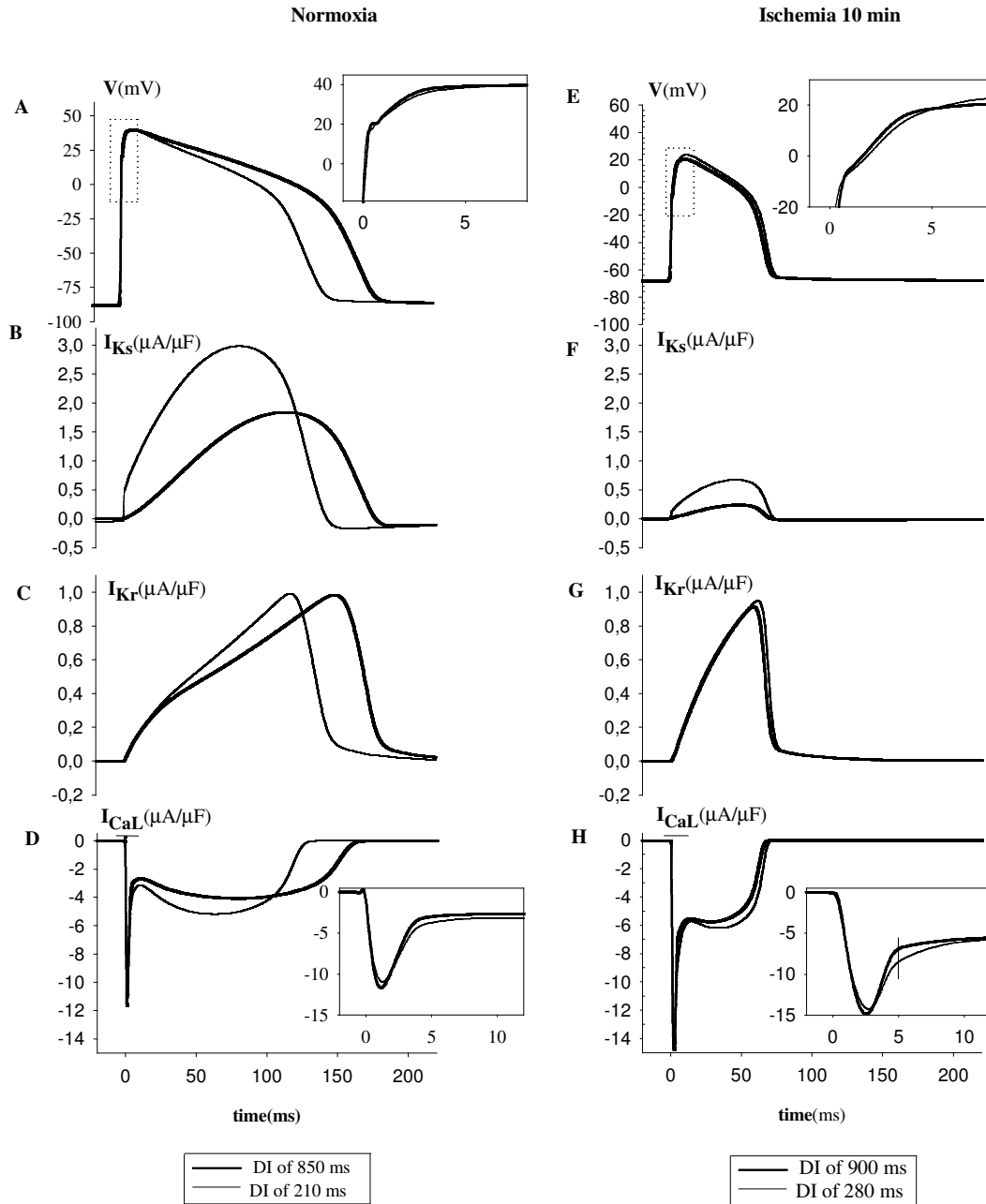As for ischemia, panels E through H of Figure 3 depict APs and the time course of ionic currents corresponding

Normoxia

Ischemia 10 min

Figure 3. Action potential, I_{Ks}, I_{Kr} and I_{CaL} during normoxia (panels A, B, C and D respectively) and action potential, I_{Ks}, I_{Kr} and I_{CaL} at 10 minutes of ischemia (panels E, F, G and H respectively)

to both situations, high DI (900 ms) and low DI (280 ms). As noted previously, both APDs are very similar, being slightly longer at a DI of 280 ms and starting to differ at 5 ms after AP onset (see zoom). As far as I_{Kr} is concerned, like in normoxia, its time course seems to be dependant on AP changes, as differences of I_{Ks} in both DIs appear much later than at 5 ms. Regarding I_{CaL} and I_{Ks}, both of them are higher at lower DIs, like in normoxia, but the respective values are very different, for instance, at 5ms the I_{CaL} increases in 2.24 µA/µF, more than three times normoxia value, while I_{Ks} increases only 0.2 µA/µF, about a quarter of its value in normoxia. This smaller increment in I_{Ks} concomitant with the far bigger one in I_{CaL} reduces APD differences between long and short DIs. Therefore, it seems that I_{CaL} is the cause of the ERC flattering in acute ischemia.

4. Discussion and conclusions

This paper is an extension of the work by Zeng et al. [12]. While that article studied the ionic mechanisms responsible for ERCs morphology in normoxia, this work studies those for acute ischemia.

Many studies have analyzed the relationship between ERC and VF, on the one hand, and the relationship between VF and ischemia, on the other hand. However, the lack of works treating ERC and ischemia directly is the motivation for this work.

Our results show that ischemia shifts ERC downwards and also produces a significant flattening of these curves. The ionic mechanism responsible for this flattening may be the increase of I_{CaL} provoked by the alteration of $[Ca^{2+}]_i$.

Acknowledgements

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