Dynamic Computational Simulations of Alternans in Acute Myocardial Ischemia

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Abstract

Action potential (AP) changes occurring in ischemic myocytes predispose the myocardium to fibrillation and sudden death. Ischemia is a critical and unstable condition, so experiments are difficult to conduct at the cellular level in human. The aim of this work is to use computational models to investigate the dynamic changes in human ischemic myocardium at the cellular level.

An ischemia-adapted version of the ten-Tusscher model of the human AP was used to simulate the electrical activity of a ventricular myocyte under ischemic conditions that were changed continuously over time, mimicking the dynamic and progressive changes in K^+, ATP and ADP concentrations and pH typical of acute ischemia.

The results show that, as expected, AP duration is reduced during the ischemic period (among other changes in the AP). Intriguingly, strong alternans begin to occur in the 3rd ischemic minute. The upstroke of the larger APs is divided into two phases, the first being maintained by Na^+ current while the second is dependent on Ca^{2+} current. The shorter APs lack the Ca-dependent phase, suggesting that irregular Ca^{2+} cycling is responsible for the electrical alternans. Alternans are abolished from the 8th minute onwards. This severe alternation in APs could introduce a large degree of heterogeneity in the tissue which could become a substrate but also a trigger for VF.

1. Introduction

Acute myocardial ischemia provokes drastic changes in the electrical behavior of cardiac cells, and in particular in the cellular action potential (AP). Some of these changes are arrhythmogenic, as they alter cell excitability and increase the probability of reentry [1]. In particular, spatial as well as temporal dispersion of action potential duration (APD) in the tissue sets the stage for unidirectional block and reentrant arrhythmias. In this respect, ischemia-induced electrical alternans [1-4] may be an important cause of temporal heterogeneity in APD.

Myocardial ischemia is a critical and unstable condition, so experiments are difficult to conduct in human at the cellular level. In the past two decades, mathematical modelling and computational simulations have been a powerful tool used to better understand ischemic dynamic processes, both at the cellular level and the tissue/organ level (see [5] for review). However, most of the simulations of ischemia are static in the sense that only several seconds of electrical activity are simulated (and not the whole ischemic period, which lasts for several minutes). This is particularly true in the tissue/organ simulations, due to the high computational demands of the models used, but is also common in cellular simulations with few exceptions [6].

The aim of this work is to theoretically investigate the dynamic changes that occur in the action potential of isolated ventricular human myocytes during simulated progressive ischemia in long-term (15 minute) simulations. In particular, the development of electrical alternans has been studied, and their causes and triggering factors have been analysed.

2. Methods

A modified version of the ten Tusscher model of action potential and ionic currents [7] was used to simulate the electrical activity of an isolated human ventricular myocyte during the acute phase of myocardial ischemia (phase IA). The model was modified to account for ischemic changes by adding the ATP-sensitive K^+ (K_{ATP}) current, which partially activates during ischemia, according to the model by Ferrero et al [8]. Also, the dependence of the Na^+/K^+ pump [9] and the SERCA pump [10] on intracellular ATP concentration was included in the model. The effects of intracellular pH on inward currents was also introduced [11].

To investigate the electrical dynamic changes in the cell, 15 minutes of electrical activity were simulated. The first 5 minutes of each simulation correspond to the control (normoxic) situation, and the values of the

relevant electrophysiological parameters of the model were kept constant with their normal values in this stabilization period. The virtual cell was paced with a basic cycle length (BCL) of 1 second with rectangular pulses 2 milliseconds in duration and twice diastolic threshold in amplitude.

After this steady-state period, progressive acute ischemia was introduced in the model. The dynamic time-course of ischemia during 10 minutes was simulated by (a) linearly increasing extracellular K^+ concentration $[K^+]_o$ (from 5.4 to 12.5 mmol/L) during the first 5 minutes of the ischemic period (see Figure 1A) and then plateauing $[K^+]_o$, and (b) decreasing intracellular pH (from 7.2 to 6.2) and intracellular ATP concentration (from 6.8 to 4.2 mmol/L) and increasing intracellular ADP concentration (from 15 to 100 μmol/L) during the whole 10 minute ischemic period. These data and time-courses were taken from Reference 11. The cell was paced at different rapid tachycardial rhythms in different simulation runs.

Action potentials, ionic currents and ionic concentrations were monitored during the whole 15 minutes of simulation. APD was measured at 90% repolarization (APD_{90})

3. Results and discussion

In the first simulation, pacing frequency was linearly increased from 60 bpm to 180 bpm during the first minute of ischemia and maintained at 180 bpm for the rest of the ischemic period, mimicking a tachycardia.

Figure 1 (panels B, C and D) depicts the time-course of the three main features of the AP during the 15 minute simulation period. As shown in Figure 1B, the resting potential of the cell progressively becomes less negative, which is a direct consequence of extracellular K^+ accumulation (see Figure 1A). Figure 1C shows the evolution of APD_{90}. A rapid decay is seen in the first minute of ischemia (minute 5 to 6) which is due to a combination of two causes: the progressive activation of K_{ATP} channels and the rapid increase in frequency. From minute 6 to minute 8 approximately, APD_{90} suffers a slower decay due to the former cause. Then, at a certain instant near minute 7.94 (green thick line in the x-axis), a bifurcation in APD90 occurs and APs begin to alternate in duration, with the long ones having an APD_{90} in the range of 200 milliseconds (with a subsequent sustained decrease due to the progressive K_{ATP} channel activation) and the short ones in the range of 40 milliseconds. This 1:1 pattern stabilizes until minute 11 approximately, when, a more complex pattern develops with 1:2:1 or even 1:3:1 alternations.

Figure 1D shows that the alternations in APD_{90} are concomitant to alternations in the peak-to-peak amplitude of the AP (V_{pp}).

In order to understand the causes of the onset of alternans, we monitored and analyzed APs and selected ionic currents and concentrations around the instant in which alternans begin to develop (green short and thick line in the x-axis in Figure 1C). The results are shown in Figure 2. The first two APs in Figure 2A (termed AP_1 and AP_2) correspond to the last "normal" (non-alternating) APs, while the third AP (AP_3) is the first "short" one, followed by two consecutive APs (AP_4 and AP_5) which begin to alternate in duration and amplitude. This alternation remains stable for several minutes, as discussed earlier.

This ischemic AP alternation in duration and amplitude is much stronger than non-ischemic (or even ischemic) experimentally observed alternans reported in the literature (see [12] for review). However, the kind of alternations found in our simulations do resemble the ones found by Kleber et al [4] in regionally and acutely ischemic pig hearts (see their Figure 2). Before the alternans begin (AP_1, and AP_2) the upstroke of the AP is divided in two phases. The first part of the upstroke, but not the second, is present in the short APs (AP_3, AP_5 and so on), which is responsible for the "short" nature of these APs. This morphology of the alternating APs is different from the one obtained in previous simulation works [13, 14], but similar to that obtained by Carro et al [15] using a modified version of the ten Tusscher 2006 model [7]. However, the simulations carried out in Reference 15 correspond to static short-term simulations and thus the mechanisms of alternans onset cannot be analyzed.

To better understand the intimate causes of the onset (and maintenance) of these alternans, we analyzed the inward currents in the model. Figure 2C shows the time-course of the fast inward Na^+ current (I_{Na}) As seen in the figure, it is clear that I_{Na} has essentially the same peak value in the last two "long" (AP_1 and AP_2) and the two "short" (AP_3 and AP_5) action potentials, suggesting that it has almost no responsibility in the alternating phenomenon. Indeed, the four mentioned APs have an almost identical first phase of the upstroke (Figure 2A). The fact that AP_2 and AP_3 (the first two APs that alternate) have an almost identical I_{Na} current suggests that this current does not provoke the onset of alternans.

Conversely, the inward L-type Ca^{2+} current (I_{CaL}, shown in panel D) shows profound differences between the APs analyzed. In the third AP (the first "short" one), the second peak of I_{CaL} which is present in the first two APs is absent, and the result is that the second phase of the AP upstroke is abolished and the AP is profoundly shortened and its amplitude is significantly reduced. These results are in accordance with previous simulations in human hyperkalemic cells [15].

After the first "short" AP has been elicited, the next action potential (AP_4) has an increased I_{Na} current, which is due to the fact that the diastolic interval between AP_3 and AP_4 is higher. Thus, this AP has a steeper upstroke (see Figure 2A) and a larger duration, which is clearly

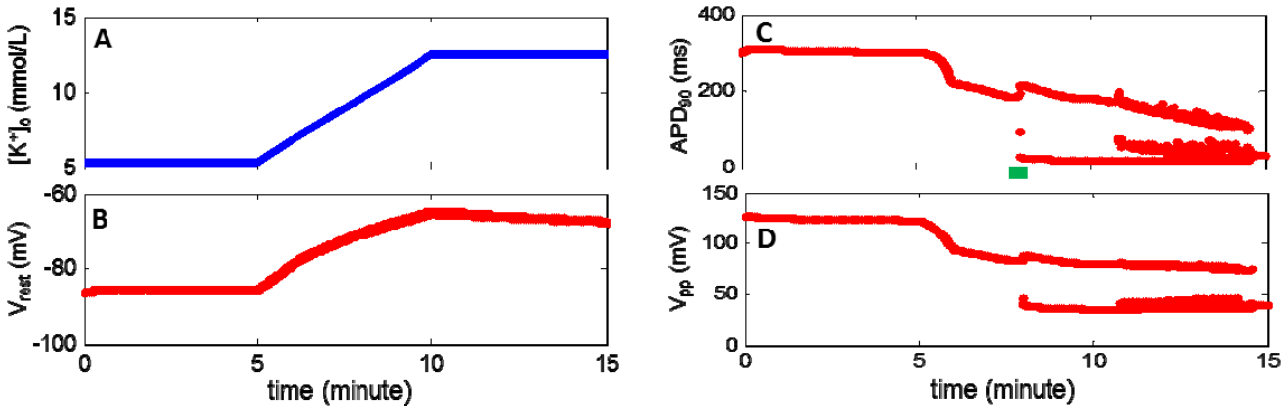

Figure 1. Time course of relevant parameters during the 15-minute simulation: $[K^+]_o$ (panel A), an input in the model, and resting potential (panel B), action potential (AP) duration (panel C) and peak-to-peak AP voltage (panel D), outputs of the model.

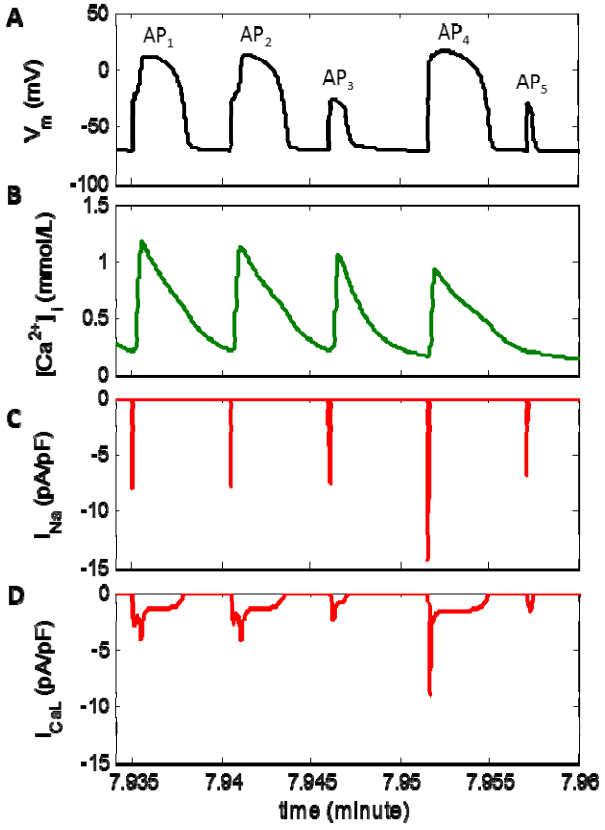

Figure 2. Action potentials (panel A), Ca^{2+} transients (B), inward Na^+ current (C) and L-type Ca^{2+} current (D) at the time of the alternans onset.

shown in Figure 1C (abrupt increase in APD_{90} around the green line). This in turn reduces the diastolic interval of the subsequent action potential (AP_5), which is thus much shorter than AP_4 (and even AP_3). This extra-shortening of the fifth AP abolishes the associated Ca^{2+} transient (shown in Figure 2B). This pattern then reaches a steady state, and stable alternans develop for several minutes (Figure 1C).

Different simulation runs were carried out for different cardiac frequencies. For pacing frequencies higher than 85 bpm, alternans did occur, but the onset was delayed for shorter frequencies. However, for cardiac frequencies smaller than 80 bpm no alternans phase was obtained.

4. Conclusions

According to our simulation results in isolated ventricular human myocytes, the onset of the alternans period during phase IA of myocardial ischemia is related to the inability of I_{CaL} current to maintain the second phase of the AP upstroke. A cardiac frequency higher than 80 bpm is needed for alternans to develop. In conclusion, long term continuous simulations can unravel the basic mechanisms of the onset of temporal heterogeneity in acute ischemia, which can set the stage for the onset of lethal arrhythmias.

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