Effects of Acute Myocardial Ischemia in Mathematical Models of Heterogeneous Myocardium

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Abstract

It has been shown that isolated sub-epicardial (EPI) and sub-endocardial (ENDO) myocytes have distinct electrical and mechanical properties in normal heart ventricle and differently respond to interventions. We utilized our electromechanical models of EPI and ENDO myocytes to simulate their responses to the acute ischemia and to predict effects of cell electromechanical coupling within a heterogeneous 1D tissue model. Intracellular effects of acute ischemia were simulated via a combination of two hypoxic consequences - a time-dependent increase in $[K^+]_o$ and a reduction in $[ATP]_i$ which affected the activity of ATP-sensitive and other potassium channels. In cellular models we showed that the higher sensitivity of ATP -sensitive potassium currents provided for a greater action potential (AP) shortening and force decrease in EPI versus ENDO cells under hypoxia. In a 1D heterogeneous myocardial strand comprising segments of EPI, ENDO and intermediate cell type, the hypoxic consequences also resulted in a decrease in the force production, while the dispersion of repolarisation between the coupled cells increased significantly above the difference in AP duration in uncoupled cells. Our modeling results suggest significant increase in the transmural electrical and mechanical heterogeneity between isolated cells under hypoxia, which further increases due to cell interactions within the tissue creating substrate for arrhythmia.

1. Introduction

Myocardial heterogeneity is the essential property of normal heart and plays a role in cardiac pathology. There is large evidence that cardiomyocytes from EPI and ENDO layers of the left ventricle (LV) differ in their electrophysiological, biochemical and mechanical characteristics [1], and respond differently to pharmacological and pathological interventions [1, 2]. Particularly, it has been reported on distinguishing responses of ENDO and EPI myocardial regions to ischemic conditions [2, 3]. ENDO regions were shown to be more vulnerable to metabolic changes during ischemia. More often, ischemic injury occurs at first in ENDO regions, then progressing toward EPI regions over time [2]. However, during acute ischemia such effects as a decrease in the action potential (AP) duration and an increase in the refractory periods, and a decrease in the conduction velocity throughout the tissue may be more prominent in EPI layers [3]. These ischemia consequences may further facilitate emergence of reentrant arrhythmias. The intracellular mechanisms of distinct ischemia-induced electrophysiological and mechanical responses of ENDO and EPI cardiomyocytes are still not clear, and will be addressed in this paper with the help of mathematical models.

It is well known, that abrupt arrest of coronary blood supply of myocardium causes in a cumulative depletion of ATP concentration ($[ATP]_i$) in cardiomyocytes. ATP depletion activates outward current $I_{K(ATP)}$ through ATP-sensitive potassium (K_{ATP}) channels, resulting in K^+ accumulation in the extracellular space (hyperkalemia). In turn, an increase in the extracellular K^+ concentration ($[K^+]_o$) alters cardiac electrical activity resulting in a reduction of the membrane excitability, shortening of AP duration, and prolongation of the recovery period of excitability [2]. Experiments in single ventricular myocytes isolated from ENDO and EPI layers have shown a greater sensitivity of $I_{K(ATP)}$ to ATP level in EPI cells, which may contribute to their more pronounced electrical responses to acute ischemia [3].

To assess how the difference in ATP-sensitivity of K_{ATP} channels in ENDO and EPI cells may affect their electrical and mechanical activity under ischemic conditions, and to change the overall electromechanical function of the tissue composed of such cells, we utilized our mathematical models of single ventricular ENDO and EPI cells and a 1D continuous model of heterogeneous myocardial tissue comprising these cellular models.

Although intracellular and extracellular acidosis is also known to accompany myocardial ischemia [4], in this paper we will not take these consequences into account and will simulate effects of 15 minutes ischemia via a combination of time-dependent effects of increased $[K^+]_o$ and reduced $[ATP]_i$.

2. Methods

2.1. Mathematical models

Earlier we have developed mathematical models of the electrical and mechanical activity in EPI and ENDO cardiomyocytes from the LV wall of guinea pig [7, 8]. These ENDO and EPI cellular models allowed us to reproduce specific features of the ionic mechanisms of AP generation, intracellular calcium dynamics and mechanics for each of cellular subtype. In accordance to the experimental data, the EPI model produces significantly shorter AP, faster Ca^{2+} transient and faster contractions with shorter time to peak contraction and lower rate constant of relaxation in both heavy-loaded isometric twitches and low-loaded isotonic contractions, as compared to the ENDO model (contrast the control data in figures 2 and 3, and see our papers [5, 6]).

The ENDO and EPI cellular models were utilized within a 1D continuous medium model, describing a strand of heterogeneous myocardial tissue comprising mechanically and electrically coupled cardiomyocytes [7]. One third of the tissue strand consisted of ENDO models, one third - of EPI models. In the middle segment, parameters of the models were gradually distributed between ENDO and EPI values. We studied isometric contractions of a strand 25.3 mm long being 26% pre-stretched from the slack length and having the initial sarcomere lengths of 2.1 μm throughout the tissue (figure 4). Depolarization wave was initiated in the ENDO edge of the tissue at 1 Hz pacing rate, and spread out with ≈ 0.6 m/s along the tissue from the ENDO towards EPI region.

2.2. Simulation of cell responses to the acute ischemia

To simulate cellular effects of the acute ischemia we used experimental data on the progressive time-dependent change in $[ATP]_i$ and $[K^+]_o$ levels in myocardium during first 15 minutes of the acute ischemia (table 1, [8, 9]).

Table 1. Input model parameters of time-dependent changes in $[ATP]_i$ and in $[K^+]_o$ during 5, 10, and 15 minutes of the acute ischemia. Adapted from [8, 9].

Ischemia, min	*$[ATP]_i$, mM*	*$[K^+]_o$, mM*
0	6.80	4.00
5	6.12	5.60
10	4.76	7.80
15	3.40	9.40

On the cellular level, the gradual changes in $[ATP]_i$ and $[K^+]_o$ levels cause a progressive increase in the activity of the ATP-sensitive K^+ current $I_{K(ATP)}$ in cardiomyocytes. Moreover, hyperkalemia may affect other K^+-dependent currents, which in turn must be followed by modulations of AP parameters.

We used a description of $I_{K(ATP)}$ from [4]:

$$I_{K(ATP)} = g_{K(ATP)} \cdot P_{ATP} \cdot \left(\frac{[K^+]_o}{4.0}\right)^n \cdot (V - E_K) \qquad (1)$$

where $g_{K(ATP)}$ = 0.0048 μS – is the maximum conductance at $[ATP]_i$ = 0 mM which was set identical in ENDO and EPI models [3]. P_{ATP} is the open probability of the K_{ATP} channel at a given ATP concentration (see eq. 2), n = 0.24 – model parameter, V – membrane potential; E_K – K^+ reversal potential.

According to [4], P_{ATP} dependence on $[ATP]_i$ can be described in terms of the following Hill-equation:

$$P_{ATP} = \frac{1}{1+\left(\frac{[ATP]_i}{k_{0.5}}\right)^h}, \qquad (2)$$

where $k_{0.5}$ is the $[ATP]_i$ at which 50% of the K_{ATP} channels are open (half-maximal saturation point); h is the Hill coefficient.

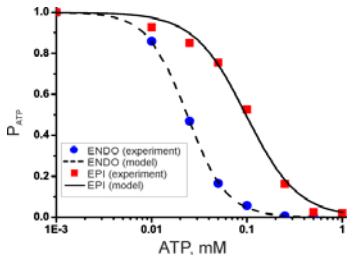

Figure 1. Dependence of P_{ATP} on $[ATP]_i$ in ENDO and EPI cells registered in experiments (*dots,* adapted from [3]) against the model fit (*lines*).

Experimental study of the K_{ATP} channel sensitivity to $[ATP]_i$ by exposure of 1 mM cyanide in ENDO and EPI myocytes revealed significantly higher activity of K_{ATP} channels in EPI cells than in ENDO cells [3] (figure 1).

We used the Hill equation (2) to fit these experimental data (figure 1). The half-maximal saturation point $k_{0.5}$ is higher in EPI than ENDO cells ($k_{0.5}$ = 0.098 mM in EPI vs $k_{0.5}$ = 0.024 mM in ENDO), specifying higher sensitivity of EPI cells to $[ATP]_i$ decrease. On the contrary, the Hill coefficient h is higher in ENDO cells (h = 2.09 in ENDO vs. h = 1.59 in EPI), so the Hill curves come closer near the $[ATP]_i$ saturation levels.

The equation (1) for $I_{K(ATP)}$ together with Hill-equations (2) and data from table 1 were utilized in ENDO and EPI cellular models to simulate the gradual

changes in the electrical and mechanical activity of the cells after the onset of myocardial ischemia (figures 2-4).

3. Results

3.1. Hypoxia effects on the electromechanical activity of single ENDO and EPI cells

Figure 2 shows the time course of AP development (left panels) and $I_{K(ATP)}$ current (right panels) during isometric contractions of ENDO and EPI cells at different exposure time to hypoxia.

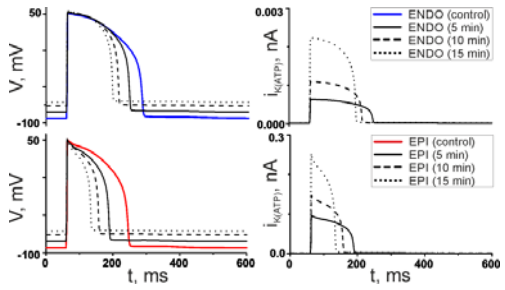

Figure 2. Time course of the membrane potential (V, *left*) and $I_{K(ATP)}$ current (*right*) during isometric twitches at pacing rate of 1 Hz in ENDO and EPI models under normal conditions (*blue* and *red* lines) and after the first 5, 10 and 15 minute of the acute hypoxia.

Both in ENDO and EPI models the amplitude of the $I_{K(ATP)}$ increased with a time exposure to hypoxia. Due to the higher ATP-sensitivity of P_{ATP} in the EPI model the amplitude of $I_{K(ATP)}$ in the EPI cell is about 2-fold higher as compared to the ENDO cell (figure 2, right panels).

Table 2. Relative shortening in APD_{90} (expressed as a percentage of the control APD_{90}) obtained in isolated rabbit ventricular myocytes during ischemia (adapted from [12]) in ENDO and EPI models.

Hypoxia, min	*ENDO (exp.), %*	*ENDO (model),%*	*EPI (exp.), %*	*EPI (model),%*
5	12.8	15.4	19.9	30.5
10	16.3	31.3	24.4	47.6
15	19.6	37.9	55.8	59.9

An increase in $I_{K(ATP)}$ with hypoxia prolongation resulted in a progressive AP shortening in both models (figure 2, left panels). In the EPI model a higher activation of $I_{K(ATP)}$ correlated with a greater shortening of AP duration versus that in the ENDO model, which qualitatively consisted with the experimental data [2, 10].

The AP duration difference between ENDO and EPI cells increased from 40 ms in normal conditions to 66 ms at 15 minute of hypoxia showing a significant increase in the electrical heterogeneity between the cells. Table 2 shows data on the relative shortening of AP duration at 90% repolarization (APD_{90}) during ischemia registered in experiments [10] and produced by ENDO and EPI models. Note that modeling results are in good qualitative agreement with the experimental data, while quantitatively both ENDO and EPI models demonstrate higher sensitivity to hypoxia as compared to the experiments.

Both ENDO and EPI models revealed a progressive diastolic depolarization due to the increase in $[K^+]_o$ during hypoxia (figure2, left panel), which might be a substrate for arrhythmia onset. At the same time, we did not obtain significant quantitative differences in the $[K^+]_o$–dependent resting potentials between the cell subtypes.

The electrophysiological effects of hypoxia were accompanied with a significant reduction in the force production in both models (figure 3). The EPI model demonstrated greater changes in the amplitude and the velocity of force development and relaxation as compared to the ENDO model. In 15 minutes of the acute hypoxia, the isometric peak force decreased by 30% in the EPI model against a 13% decrease in the ENDO model. A decrease in the time to peak force (TTP) and characteristic time to 70% relaxation (TR_{70}) is more pronounced in the EPI versus ENDO cell model (e.g. in 15 min of acute hypoxia, 12% decrease in ENDO model vs. 20% in EPI model for TTP and 8% vs. 51% for TR_{70}). Mechanical distinctions between the cells were in line with a greater decrease in the amplitude of calcium transient in the EPI model following the more prominent shortening of AP, which altered potential-dependent Ca^{2+} currents more substantially in the EPI cells.

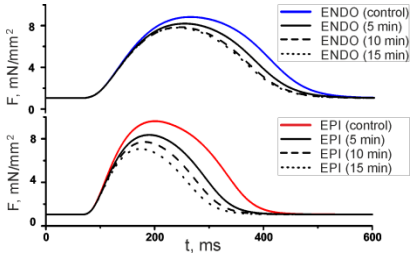

Figure 3. Isometric tension (F) generated by ENDO (*top*) and EPI (*bottom*) cellular models under normal conditions and during the first 15 minutes of the acute hypoxia.

3.2. Effects of hypoxia in 1D tissue model

Figure 4 shows time course of excitation and isometric twitch developed in the 1D tissue model in the control condition (left panels) and in 15 minutes of the hypoxia (right panels).

In the coupled cells of the tissue maximum AP upstroke velocity (dV/dt_{max}) decreased in both ENDO and EPI cells by about 25% in 15 minutes of hypoxia as in uncoupled cells. Gradient in the upstroke velocity throughout the tissue increased as compared to that in the control tissue. Similarly with isolated cells, the coupled cells demonstrated significant diastolic depolarization and a decrease of the AP duration along the strand in hypoxia. Relative shortening in APD_{90} was of 41.2 % in ENDO cells and of 61.7 % in EPI cells in 15 minutes of hypoxia exceeding that of isolated cells (table 2) and provided for the dispersion of repolarisation of 25 ms in the ischemic tissue (figure 4, top panels). We obtained a 14 % decrease in the isometric force, a 13 % decrease in the TTP and 5% decrease in TR_{70}, generated by the ischemic model against the control force (figure 4, bottom panels).

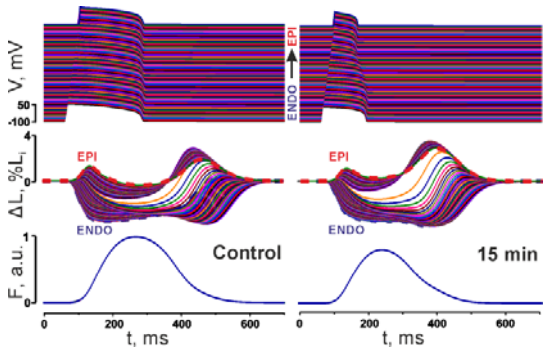

Figure 4. Effects of the acute hypoxia in the 1D continuous tissue model. *Top*: membrane potential (V) in cells along the strands (excitation spreads from the bottom ENDO to the top EPI segments). *Middle:* regional cell deformations (ΔL, % of the initial length L_i). *Bottom*: normalized isometric tension (F) generated by the strands.

4. Discussion

Modeling results suggest a significant increase in the transmural heterogeneity of the electrical and mechanical activity of EPI and ENDO cells under hypoxia, which is consistent with experimental data [2, 10]. Distinguishing ATP-sensitivity of $I_{K(ATP)}$ currents in ENDO and EPI cells allows models to reproduce greater electrical effects and to predict greater mechanical effects of hypoxia on EPI cells as compared to ENDO cells. The experimental data and our model simulations suggest that despite the ENDO cells are more vulnerable to ischemic injury *in vivo* due to the specific regional cardiovascular blood supply, *in vitro* the ENDO cells demonstrate a lower sensitivity to hypoxic interventions assuming their better adaptation. In the tissue model, ischemic changes in the cellular activity result in further increase in the electrical heterogeneity between coupled cells, which caused the dispersion of repolarisation to appear providing for a substrate for arrhythmia. Surprisingly, that an increased electrical heterogeneity between the cells in the ischemic tissue was not followed by a greater negative effect of cell coupling on the force production which was about the same value as in isolated ENDO cells, but less than that in isolated EPI cells. So, the dynamical stretch of later activated EPI cells due to the mechanical interactions between the cells in the tissue allowed for some contractile compensation as compared to isolated cells.

Acknowledgements

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