Modeling of Heterogeneity in Electrical and Mechanical Properties of Guinea Pig Ventricular Myocytes

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Abstract

Heterogeneity of myocardium proved to be important for understanding heart physiology and pathophysiology. In contrast to a number of papers addressing the electrophysiological heterogeneity of cardiomyocytes, much less is known about heterogeneity of their mechanical function. The aim of this study was to develop mathematical models of the electrical and mechanical function of cardiomyocytes from sub-epi- and sub-endocardial ventricular layers that take into account specific features of intracellular mechanisms underlying pronounced regional differences in the functional properties of the cells in guinea pig. Using the developed models we quantitatively tested several hypotheses on possible contribution of the transmural gradient in Na^+/Ca^{2+} exchange currents to the cellular function. The simulations consist with a hypothesis that transmural gradient in Na^+/Ca^{2+} exchange currents may partially result from the heterogeneity in Na^+/K^+ pump in cells from different transmural regions.

1. Introduction

The electrical and mechanical activity of ventricular cardiomyocytes is known to vary depending on the spatial location of cells in the wall, in particular, from sub-endocardial (ENDO) to sub-epicardial (EPI) layer. A number of studies were focused on the heterogeneity of the ionic currents and certain protein isoforms in cardiomyocytes across ventricular wall [1-3], but much less is known about heterogeneity of the cellular mechanical function [4] and underlying mechanisms of excitation-contraction coupling. Particularly, experimental data on the regional differences in Na^+/Ca^{2+} exchange are controversial. It was shown that Na^+/Ca^{2+} exchange current (I_{NaCa}) is significantly higher in EPI myocytes in murine heart [5], whereas a higher I_{NaCa} is registered in ENDO cells in rabbit heart [6]. Wang and co-authors did not find differences in expression of Na^+/Ca^{2+} exchange proteins within canine left ventricular (LV) wall, while revealed a transmural gradient in Na^+/K^+ pump currents (I_{NaK}) and corresponding $[Na^+]_i$ [7]. The authors suggested that transmural gradient in I_{NaCa} may be generated by a transmural gradient in the expression of the Na^+/K^+ pump [7].

Here, we present our recent mathematical models of the electro-mechanical coupling in cardiomyocytes from ENDO and EPI transmural layers of the guinea pig LV wall taking into account heterogeneity of both the electrical and mechanical characteristics and several parameters of excitation-contraction coupling in cardiomyocytes. These models are used to study effects of transmural gradient in I_{NaCa} arising from different causes on the electrical and mechanical function of ENDO and EPI cells.

2. Model description

Recently we have developed integrative mathematical models of the electrical and mechanical activity in cardiomyocytes from sub-endocardial (ENDO model) and sub-epicardial (EPI model) layers of the LV wall of guinea pig during the cardiac cycle [8]. The models are based on the Ekaterinburg-Oxford mathematical model (EO-model) accounting for the ionic and myofilament mechanisms of excitation-contraction coupling in cardiomyocytes [9]. The EO-model was used to simulate the electrical and mechanical activity of cardiomyocytes in the different experimental conditions. The CellML-model representation can be found at http://models.cellml.org/e/b9/ and run with using Cellular Open Resource at http://cor.physiol.ox.ac.uk/ [10]. A key feature of the model is inclusion of the cooperative dependence of thin filament Ca^{2+} activation, particularly the dependence on the concentration of attached crossbridges, assuring a key molecular mechanism of the mechano-electric feedback in cardiomyocytes.

It should be noted that mechanisms underlying the regional differences in action potentials (AP) and contractions in cardiomyocytes from different ventricular layers of guinea pig differ from those of other species. In particular unlike rat, dog and human, where regional distinctions in the transient outward current (I_{to})

contribute significantly to the differences in AP shape and duration, this current is almost absent in guinea pig cardiomyocytes [2], resulting in the lack of AP spike-and-dome morphology (especially in EPI cells) and suggesting other contributors to the cellular electrical heterogeneity. Our ENDO and EPI models take into account these specific features of the electrical function in cardiomyocytes of the guinea pig. We used a number of experimental data [2-4,11,12] to modify parameters in the equations of the electrical and mechanical blocks of the EO-model.

First, we fitted model parameters to simulate experimental data on the transmural differences in the rapid and slow components of delayed rectifier potassium currents (i_{Kr} and i_{Ks}) [2], and took into account the regional differences in the persistent sodium current as suggested in [3]. Consistent with experimental data, this resulted in a shorter AP generated by the EPI model as compared with the ENDO model.

Nevertheless, the changes in electrophysiological parameters only did not allow the EPI model to simulate significantly faster descending phase of Ca^{2+} transient and faster contractions against the ENDO model as observed experimentally in isolated cardiomyocytes [12]. To simulate these regional differences between cardiomyocyte function, some specific parameters of cellular mechanics and Ca^{2+} handling were also modified in the models. Following the data on the higher density of the calcium pump proteins (SERCa) of the sarcoplasmic reticulum (SR) in EPI cardiomyocytes [11], we decreased the maximal velocity of the SR pump in the ENDO model. Then, we increased in the EPI model parameters that determine the maximal velocity of unloaded sarcomere shortening and the rate constants of cross bridges attachment and detachment in the steady-state conditions, and also increased the probability for myosin head to find active sites on the actin filament. The parameter changes provided with a higher rate constant of cross bridges cycling in the EPI model, which is consistent with the data obtained in guinea pig skinned cardiomyocytes demonstrating that the rate of tension redevelopment after quick release is higher in EPI cells compared with the ENDO cells [4]. Moreover, consistent with experimental data suggesting a weaker molecular cooperativity of contraction generation in EPI versus ENDO cells [4], we changed certain model parameters to reduce the degree of cooperativity in the interactions between the myofilaments, regulatory protein troponin C and cytosolic Ca^{2+} in the EPI model.

As a result, our EPI model produces significantly shorter action potential, faster Ca^{2+} transient, and faster contractions with smaller time to peak contraction in both heavy-loaded isometric and low-loaded isotonic modes of contractions, as compared to the ENDO model (figure 1, control models) Note, that the differences in the mechanical activity produced by the ENDO and EPI models via mechano-electric feedback mechanisms accounted for in our models enhanced further the difference in the AP duration as compared with the models with only electrophysiological parameters modified [8].

The control ENDO and EPI models simulated transmural gradients in the electrical and mechanical properties of isolated cardiomyocytes from different regions of LV wall more qualitatively rather than quantitatively. More accurate quantitative simulations require additional molecular mechanisms to be involved, such as regional features of Na^+/Ca^{2+} exchange which may play a role in the cellular transmural heterogeneity.

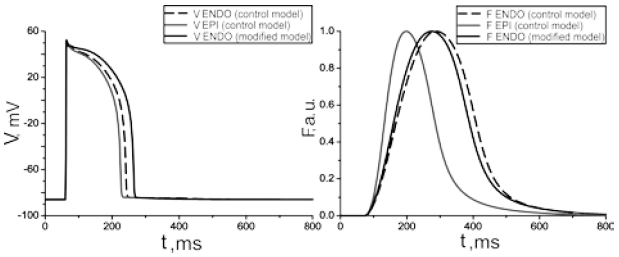

Figure 1. Action potential (V) and isometric force (F) during the cardiac cycle in the control and modified ENDO (black lines) and EPI (gray lines) models simulated at 0.5 Hz, at a cardiomyocyte length L = 0.94 L_{max}, and $[K^+]_o$ of 5.4 mM.

3. Results

We verified described above control EPI and ENDO models against experimental data on the effects of altering extracellular potassium concentration ($[K^+]_o$) on regional differences in AP parameters in ENDO and EPI cells. In experiments reported by Wan and co-authors [13] there were found regional differences in AP duration to 90% of repolarization (APD_{90}) with longer APD_{90} in ENDO cells and shorter APD_{90} in EPI cells at low, medium and high $[K^+]_o$ (figure 2, left panel, solid lines). Note, that more pronounced effect of altering $[K^+]_o$ on APD_{90} was shown in EPI cells than in ENDO cells, so the difference in APD_{90} between the cells increased with increasing $[K^+]_o$. Unlike the experimental data the differences in APD_{90} between ENDO and EPI cells were significantly less pronounced in control EPI and ENDO models especially at high $[K^+]_o$ (figure 2, left panel, dotted lines).

In order to improve the control models, we tested the following hypotheses suggested by different authors [5-7] on the role of regional differences in I_{NaCa} in the above effects of $[K^+]_o$ on APD_{90}.

There are two hypotheses tested:

1) There is a transmural gradient in I_{NaCa} due to a heterogeneity of Na^+/Ca^{2+} exchange protein expression (suggested by Xu and co-authors, Quinn

and co-authors [5,6]). In simulations we directly varied the amplitude of I_{NaCa} in either EPI or ENDO models against the control values.

2) Transmural gradient in I_{NaCa} is generated by a heterogeneity of the expression of the Na^+/K^+ pump (suggested by Wang and co-authors [7]). In modified models we varied the amplitude of I_{NaK}, which induced consequent changes in I_{NaCa}

An increase in the amplitude of I_{NaCa} in the EPI model produced insignificant changes in the APD_{90}. In the ENDO model, same increase in the amplitude of I_{NaCa} decreased APD_{90} at low $[K^+]_o$, and the differences in APD_{90} between the modified ENDO and control EPI models became almost $[K^+]_o$ independent. An increase in the amplitude of I_{NaK} in the EPI model made APD_{90} differences even less than in the control models. In only the case of an increase in the amplitude of I_{NaK} in the ENDO model, transmural differences in APD_{90} increased between the modified ENDO and control EPI models at all $[K^+]_o$ compared with the control models (figure 2, right panel). However, even in this case the APD_{90} difference between the ENDO and EPI models decreased with increasing $[K^+]_o$ due to more strong $[K^+]_o$ effect on the ENDO model. This disagreement between simulations and experiments suggests that additional mechanisms have to be accounted for to reproduce the experimental data more adequately.

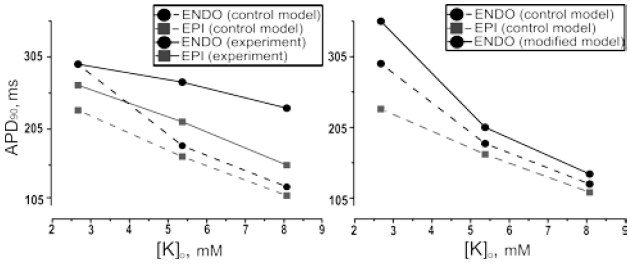

Figure 2. Experimental data [13] and model simulations showing effect of changing $[K^+]_o$ on regional differences in APD_{90} between ENDO (circle) and EPI (square) myocytes from guinea pig LV wall at three different $[K^+]_o$ (2.7, 5.4 and 8.1 mM). Action potential parameters are measured at a stimulation frequency of 0.5 Hz.

In addition to the effect on APD_{90}, we evaluated effect of altering $[K^+]_o$ on the temporal characteristics of contraction in all the tested models. In the control models, we found regional differences in the time to peak contraction (TTP) and time to 70% of relaxation (TR_{70}), with bigger TTP and TR_{70} in the ENDO against the EPI model at every $[K^+]_o$. The increase in $[K^+]_o$ produced more pronounced effect on TR_{70} in the control EPI model than in the control ENDO model (figure 3, dotted lines) consisting with the experimental data on $[K^+]_o$ effect on APD_{90} [13]. In the modified models, the only an increase in the amplitude of I_{NaK} in the ENDO model kept the similar $[K^+]_o$ effect on TR_{70} with even more expressed divergence in TR_{70} with increasing $[K^+]_o$ between the modified ENDO and control EPI models (figure 3, compare solid line and dotted lines). Thus, we believe that the second hypothesis on the transmural heterogeneity of Na^+/K^+ pump is more consistent with the specific features of the electrical and mechanical function of isolated ENDO and EPI myocytes.

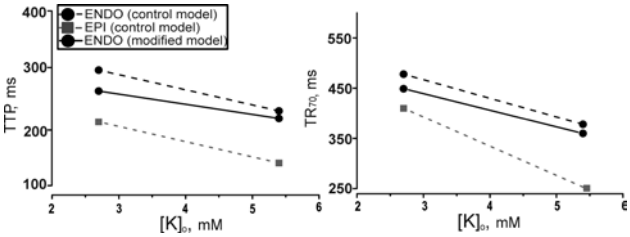

Figure 3. Effect of changing $[K^+]_o$ on the time to peak contraction (TTP) and time to 70% relaxation (TR_{70}) in ENDO (circle) and EPI (square) models. Contractions were produced along with corresponding AP (shown in Fig. 2) at a stimulation frequency of 0.5 Hz.

Our model simulations showed that an increased I_{NaK} amplitude in the modified ENDO gradually reduced the amplitude of the reverse mode I_{NaCa} with increasing $[K^+]_o$ as compared to the control ENDO model, making the difference in the I_{NaCa} between the modified ENDO and the control EPI model more expressed (fig. 4). These predictions consist with experimental data observed in canine myocytes [14]. The decrease in the repolarizing reverse mode I_{NaCa} induced the $[K^+]_o$–dependent increase in APD (fig. 2) in the modified ENDO model followed by the effects on contractions (fig. 3).

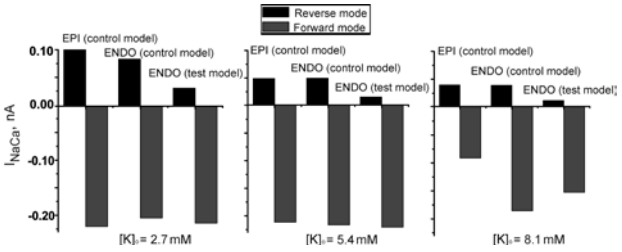

Figure 4. Amplitudes of the forward and reverse mode I_{NaCa} at $[K^+]_o$ of 2.7, 5.4 and 8.1 mM in the control EPI and ENDO models and the modified ENDO model. Amplitudes of I_{NaCa} were measured at a stimulation frequency of 0.5 Hz.

Thus, transmural gradient for the reverse mode I_{NaCa} arisen from the transmural gradient for Na^+/K^+ pump appears to contribute to the functional heterogeneity in EPI and ENDO cells at various concentrations of $[K^+]_o$.

4. Discussion

We developed improved mathematical models of the electromechanical coupling in cardiomyocytes from transmural layers of the guinea pig LV wall which reproduce physiological experimental data obtained in isolated myocardial cells. The results presented here demonstrate that mechanism of a transmural gradient in Na^+/Ca^{2+} exchange due to a transmural gradient in Na^+/K^+ pump is able to increase heterogeneity of the electrical function between EPI and ENDO models (figure 1, left panel), especially at low and medium $[K^+]_o$. Moreover, such gradient in Na^+/Ca^{2+} exchange increases the differences between the rates of contraction-relaxation with increasing $[K^+]_o$ in ENDO and EPI models.

In contrast to our model predictions on the heterogeneity of I_{NaK}, Lancaster and co-authors did not find regional differences in the levels of α1 isoform of Na^+/K^+-ATPase and activated pump current in the LV of rabbit [15], so heterogeneity of Na/K pump might be related to different levels of other isoforms.

Based on the data on the gradient in intracellular sodium concentration $[Na^+]_i$, which was lowest in sub-epicardial cells, Gao and co-authors suggested a transmural gradient in I_{NaK} with the highest I_{NaK} in sub-epicardial cells [16] rather than in sub-endocardial cells as suggested from our simulations. Our simulations suggest that regional differences in $[Na^+]_i$ with lowest $[Na^+]_i$ in sub-epicardial cells could more likely arise from the differences in influx Na^+ currents rather that due to I_{NaK}, as also assumed also by Osadchii and co-authors [17].

The controversial hypotheses derived from different experimental data should be analyzed further within the models.

Acknowledgements

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