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+/Ca2+ exchange currents to the cellular function. The simulations consist with a hypothesis that transmural gradient in Na+/Ca2+ 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+/Ca2+ exchange are controversial. It was shown that Na+/Ca2+ 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+/Ca2+ exchange proteins within canine left ventricular (LV) wall, while revealed a transmural gradient in Na+/K+ pump currents (I_{NaK}) and corresponding [Na+], [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 Ca2+ 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 (Ito)
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 rapid and slow components of delayed rectifier potassium equations of the electrical and mechanical blocks of the EO-model.

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 (APD90) with longer APD90 in ENDO cells and shorter APD90 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 APD90 was shown in EPI cells than in ENDO cells, so the difference in APD90 between the cells increased with increasing $[K^+]_o$. Unlike the experimental data the differences in APD90 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 APD90.

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
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 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 EPI model. This disagreement between simulations and experiments suggests that additional mechanisms have to be accounted for to reproduce the experimental data more adequately.

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% 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 as compared to the control ENDO model, making the difference in the $I_{NaK}$ between the modified ENDO and the control EPI model more expressed (fig. 3). 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).

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 $[K^+]_o$. 

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.

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.

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 $I_{NaCa}$ produced more pronounced effect on TR$_{70}$ in the control EPI model as compared to the control ENDO model, making the difference in the $I_{NaK}$ between the modified ENDO and the control EPI model more expressed (fig. 3). 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).
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+/Ca2+ 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+/Ca2+ 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 subepicardial cells, Gao and co-authors suggested a transmural gradient in I_{NaK} with the highest I_{NaK} in subepicardial 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 than 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.

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References


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