Mechano-Electric Feedbacks in a New Model of the Excitation-Contraction Coupling in Human Cardiomyocytes

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Abstract

The study is aimed to develop a new human cardiomyocyte model, which describes electromechanical coupling and mechano-electric feedbacks. The combined electromechanical model (TNNP+M) links the TNNP06 electrophysiological model of the human cardiomyocyte with our earlier developed model of the myocardium mechanical activity and its calcium regulation.

In the TNNP+M model, we tried to maintain principal features of calcium transients and action potentials during the twitches typical for the human cardiomyocytes.

The developed TNNP+M model allows simulating several basic classic phenomena such as load-dependent relaxation and length-dependence of isometric twitches and respective changes in action potential duration. We have also simulated some age-dependent changes in the electrical and mechanical activity in the human cardiomyocytes.

1. Introduction

Development of personalized mathematical models of the human heart has become a challenge to increase the efficiency of medical practice. Three-dimensional multiscale modeling requires careful development of cellular level models to account for intracellular mechanisms underlying the coupling between heart excitability and its pump function.

The experimental data on the electromechanical activity of the human cardiomyocyte are very limited. Mathematical models allow integrating the available scarce and scattered experimental data obtained on healthy and pathological human myocardium into the whole picture, and adapting some data obtained on experimental animals.

Several reputed models of the human cardiomyocytes describe electrophysiological function of the cells [1-5]. They are widely used for 2D and 3D modeling to study mechanisms of cardiac arrhythmia in human [6]. Two available models of the excitation-contraction coupling in the human cardiomyocytes [7, 8] combine the TNNP06 electrophysiological model [4] with the Rice [9] and Negroni-Lascano [10] models of the mechanical activity of the cardiac muscle, respectively. However, the referred studies do not provide an analysis of mechano-electric feedbacks (MEF) at the cellular level.

Meanwhile, intracellular MEF underlies an important pathway of myocardial auto-regulation adjusting its contractile function to the mechanical loading and contributing to the mechanical interactions between heterogeneous cardiomyocytes in the walls of the heart ventricles. In experiments on cardiac muscle preparations, MEF is revealed in several basic phenomena, including length-dependence of contractions and load-dependent relaxation. These and similar experiments were performed many times on papillary muscles and trabecules of various animal species (e.g. [11]). However, for obvious reasons, it is difficult to obtain similar data in human preparations. Therefore, just mathematical modeling is to be in high demand for predicting possible effects of MEF in human cardiomyocytes. We developed here such mathematical model and apply it, in particular, to simulate mechano-dependent activity of adult and aged human cardiomyocytes.

The cross-links between the electrical and mechanical activity in the new model are reproduced due to accounting for cooperative mechanisms of Ca^{2+} activation of myofilament regulatory units in the cell.

2. Methods

2.1. Mathematical model

We developed a combined electromechanical model (TNNP+M) based on the TNNP06 electrophysiological model of the human cardiomyocyte [4] and our model of the myocardium mechanical activity and calcium handling [12].

The model of mechanical activity has been developed

earlier as a component in the Ekaterinburg-Oxford (EO) electromechanical model developed for various laboratory animal cardiomyocytes [13]. Description of the cooperativity of regulatory and contractile proteins is a key feature of the EO model allowing us to explain and reproduce a wide range of mechano-calcium and mechano-electric feedbacks.

The TNNP+M model combines the electrical and mechanical equations via the equations for intracellular calcium kinetics, which is intrinsic but differently detailed part of the cellular electromechanical models. For this linkage, we had to introduce thorough description of the calcium – troponin C (CaTnC) kinetics, because it is a key mechanism of the myocardium contraction activation, whereas in the TNNP06 model this kinetics was implied only as a part of a simplified single intracellular calcium buffer. The following equation inherited from the EO model is used in the TNNP+M model for the CaTnC concentration time course:

$$\frac{d[CaTnC]}{dt} = k_{on} \cdot \left([TnC]_{tot} - [CaTnC]\right) \cdot [Ca^{2+}]_i - k_{off}([CaTnC], N) \cdot [CaTnC], \quad (1)$$

where $[TnC]_{tot}$ – total concentration of troponin C in the cell, $[Ca^{2+}]_i$ – free intracellular calcium concentration, N – fraction of force-generating crossbridges, k_{on} and $k_{off}([CaTnC],N)$ are on- and off-rate "constants" of the CaTnC complex formation. Nonlinear dependence of the off-rate on [CaTnC] and N accounts for the cooperative mechanisms of calcium activation of thin myofilaments. Detailed formulations of cooperativity mechanisms have been done and justified earlier [12]. These mechanisms are the keys to the mechano-calcium feedbacks and consequently to the mechano-electric feedbacks. Thus, the generalized buffer described reductively by a quasi-stationary algebraic equation in the TNNP06 model we replaced by differential equations for cytosol Ca^{2+} buffers including Eq. (1) for the CaTnC.

To keep the species-specificity of the TNNP06 model we maintained qualitative and even quantitative features of the Ca^{2+} transient (i.e. time course of the changes in the cytosol Ca^{2+} concentration) during the contraction-relaxation cycle by fitting parameters of Ca^{2+} kinetics. It was especially necessary as the shape and duration of the Ca^{2+} transient in the TNNP06 model determine the shape and duration of the action potential (AP) specific just for the human cardiomyocytes. To simulate time characteristics of the isometric twitch of the human cardiomyocyte obtained experimentally [14] we fitted some parameters of the mechanical component, as well.

Significant challenge of the combining of the two models was to obtain mechano-dependence of the AP duration. Analysis of model parameters showed that the sodium-calcium exchange current (i_{NaCa}), which plays an important role in MEF in the cardiomyocyte, was not sufficiently sensitive to changes in the concentration of intracellular calcium in the TNNP06 model. A parametrical tuning of the i_{NaCa} within the combined TNNP+M model allowed us to obtain a good mechanical dependence of the AP (see Results).

2.2. Simulation of aged cardiomyocyte

Data on the age-related intracellular changes in the myocardium is widely reported (e.g. [15]). The integrative effects of these changes on the electrical and mechanical activity in cardiomyocytes are still insufficiently explored [16].

Here, we used the TNNP+M model to simulate effects of age-related changes in the sarcoplasmic reticulum (SR) ATPase activity [17] on the excitation-contraction coupling in the human cardiomyocytes. To simulate the slowing down of Ca^{2+} uptake in ageing myocardium, we decreased maximal velocity of the SR pump by 50% as compared to the reference value.

All results are shown for the steady-state contractions at a pacing rate of 1 Hz.

3. Results

3.1. Load dependence of the electromechanical activity

The main experimental modes used to study mechanical activity in myocardium are isometric and isotonic twitches at different sarcomere lengths (preload) and mechanical loads (afterload). Isometric contractions develop at a fixed length of the preparation during the cycle. During the isotonic phase of the afterloaded twitch, a myocardial preparation shortens and lengthens under a fixed constant load. Figure 1 illustrates the mechanical and electrical activity and Ca^{2+} transients in the cardiomyocyte during isometric (bold lines) and afterloaded twitches under different afterloads (decreased from dark to light grey lines) in the TNNP+M model. The duration of afterloaded twitches shortens with a decrease in afterload. The end-systolic shortening of the virtual preparation increases along with an increase in the velocity of deformation under the afterload decrease.

The mechanisms of mechano-calcium and mechano-electric feedbacks reveal themselves in the prolongation of Ca^{2+} transient and AP with decreased afterload. The Ca^{2+} transient decay slows down via cooperative dependence of CaTnC kinetics on fraction of force-generated crossbridges. The slower $[Ca^{2+}]_i$ decay corresponds to the longer AP duration.

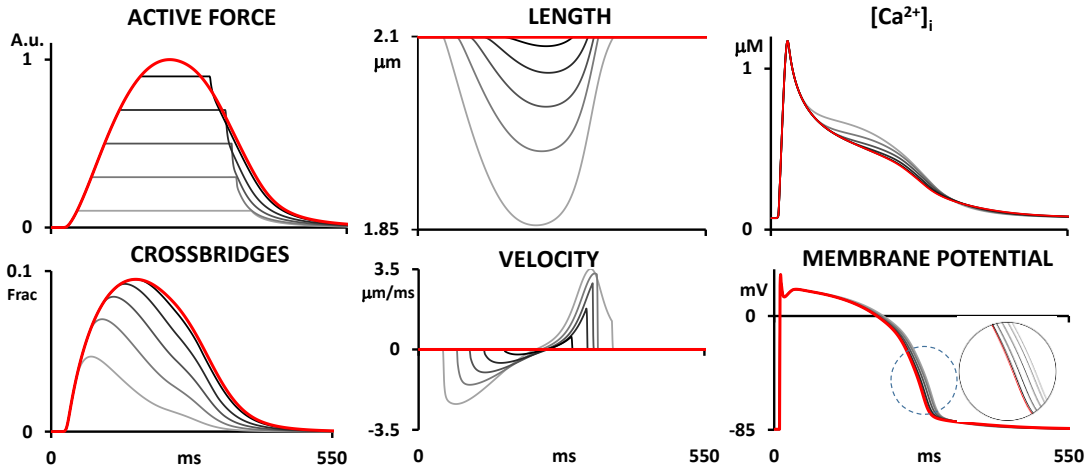

Figure 1. Afterload-dependent twitches. Bold (red) lines show the signals during isometric twitch. Lines from dark to light grey show signals during isotonic contractions under decreasing afterloads. Force values are normalized to the peak isometric value. The insert shows scaled-up differences in the AP duration under different afterloads.

3.2. Isometric twitches at different lengths

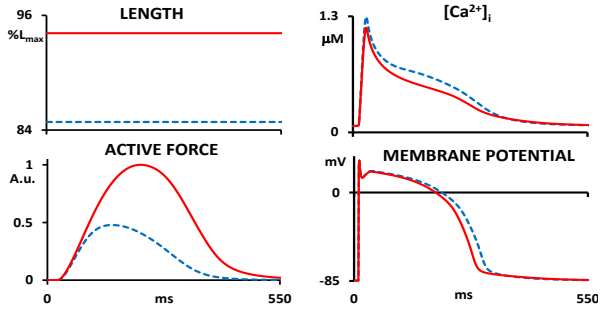

Figure 2. Preload-dependent isometric twitches. Solid (red) lines are for the bigger initial cell length as compared to the dashed (blue) lines. Force values are normalized to the peak value of the more elongated cell.

The TNNP+M model reproduces the dependence of the electromechanical activity of the cell on the initial sarcomere length (preload). Figure 2 shows the dynamic changes in the force, free cytosolic Ca^{2+} and transmembrane potential in the cell during isometric twitch at two lengths: $0.85L_{max}$ and $0.95L_{max}$ (where L_{max} is the length at which the maximum isometric force is generated). The model demonstrates significant increase in the time to and in the peak of isometric force at the higher length. Simulated Ca^{2+} transients during isometric contractions show a slightly reduced peak and shorter duration in the stretched cell. AP at the longer cell length is also shorter reflecting MEF mechanisms accounted for in the TNNP+M model. The TNNP+M model also produces mechano-calcium and mechano-electric feedback effects for various protocols of quick deformations (stretch and release) during the isometric twitch (unshown here).

3.3. Simulation of the aging

It is well documented that one of the essential change in excitation-contraction coupling with aging is a reduction in the SR Ca^{2+} pump activity [17]. Here, we tested consequences of a 50% reduction in the maximal SR pump velocity (rate-constant) in the TNNP+M model (Fig. 3). The two-fold decrease in this parameter resulted in a 30% decrease in the SR diastolic level and considerable decrease in the peak of the Ca^{2+} transient and an increase in the time to peak (Fig. 3, $[Ca^{2+}]_i$). The total amount of Ca^{2+} released from SR reduces by 50% as compared to the reference model. This was accompanied with an increase in the amount of Ca^{2+} entering the cell during excitation via i_{CaL} and i_{NaCa} by 10%. Particularly, the reverse-mode of i_{NaCa} brings 15% more Ca^{2+} to the cell as compared to the reference model (Fig. 3). An increase in external entering Ca^{2+} partially compensates Ca^{2+} unloading in the SR.

A decrease in the bulk intracellular Ca^{2+} resulted in the significant decrease in the active force produced by the ageing model (Fig. 3). The changes in the Ca^{2+} handling affected AP morphology and duration (Fig. 3, membrane potential). The 'spike-and-dome' phase became less pronounced, and AP duration increased. Both a decrease in the force production and prolongation of the AP produced by the model with reduced SR Ca^{2+} pump activity reflect these most distinctive signs of the age-related changes in the heart.

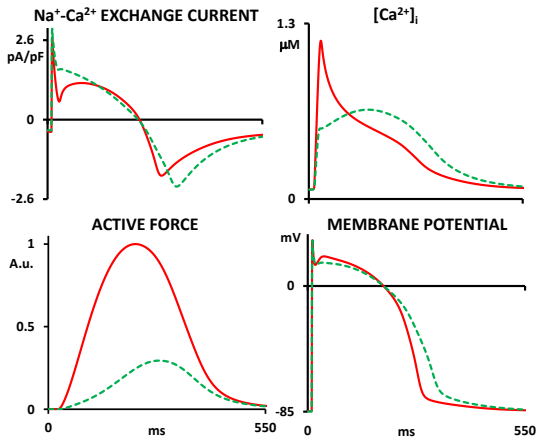

Figure 3. Age-related changes in the cardiomyocyte activity. Solid (red) lines are the signals produced by the reference model; dashed (green) lines are produced at the two-fold decrease in rate-constant of the SR Ca^{2+} pump. Force is normalized to the control peak.

4. Conclusions

The developed TNNP+M model simulates the direct and inverse relations between electrical and mechanical phenomena in the human cardiomyocytes thanks to the mechanisms of cooperativity. The TNNP+M model may be further incorporated in the multiscale models of multicellular myocardium up to that of the whole ventricles and used for systematical computational assessment of the MEF contribution to the regulation of mechanical and electrical functions in the human hearts.

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