

Investigation of Mechanisms of Regulation of Electromechanical Function of Cardiomyocytes in the Biomechanical Model of Myocardium

Vladimir Sholohov¹, Vladimir Zverev¹, Alexander Kursanov^{1,2}

¹Ural Federal University, Ekaterinburg, Russia

²Institute of Immunology and Physiology, Ural Branch of the Russian Academy of Sciences, Ekaterinburg, Russia

Abstract

We developed three-dimensional model of isolated myocardial muscular preparation that takes into account the coupling of excitation with contraction in the myocardium at the cellular and tissue levels. This model describes myocardium sample using approaches and methods developed in continuum mechanics. In the model, electromechanical interactions and mechano-electric feedbacks are realized both at the micro level and at the macro level. We used non-linear partial differential equations describing the deformation of the cardiac tissue, and a detailed “Ekaterinburg-Oxford” (EO) cellular model of the electrical and mechanical activity of cardiomyocytes. Electrical and mechanical interactions between the cells in tissue, as well as intracellular mechano-electric feedback beat-to-beat affect the functional characteristics of coupled cardiomyocytes further, adjusting their electrical and mechanical heterogeneity to the activation timing. Model analysis suggests that cooperative mechanisms of myofilament calcium activation contribute essentially to the generation of cellular functional heterogeneity in contracting cardiac tissue.

1. Introduction

There is a wide evidence on the influence of mechanical conditions and mechanical activity on electrical activity in myocardium, which is referred as the cardiac mechano-electric feedback (MEF) or in more common sense as the mechano-electric coupling [1]. Mechanical effects on excitation have been registered in isolated cells, multicellular preparations and in the whole organ. In single cells and multicellular preparations (muscle strips), both electrical and mechanical activity can be considered as spatially uniform. Such physiological experiments characterize MEF effects on micro- (intracellular) and meso- (cellular) levels. Much less is known on how these MEF mechanisms are integrated and reveal themselves on macrolevels in the

tissue and organ, where electrical and mechanical waves developing in myocardium interfere and influence each other within the entire muscle volume.

In experiments technical restrictions do not allow to observe the entire dynamical processes underlying continuous spatio-temporal electrical and mechanical interactions in the tissue during the electrical excitation wave propagation and contraction development. Nowadays, mathematical modeling appears to be the only possible tool, which may help to uncover the mechanisms of MEF integration on the tissue level [2,3].

In this study, we present a detailed electromechanical model including both intracellular and intercellular MEF mechanisms to study excitation-contraction coupling in myocardium tissue.

2. Mathematical model

As the size of the cardiomyocytes is sufficiently small compared to the heart characteristic dimensions, any cardiac cell can be considered as an isopotential point of myocardial tissue. In this case, a myocardium sample may be considered as a continuous medium where each cell (point) dynamically changes its position during the contractile cycle. The model accounts for both micro- and macro- circuits of the electro-mechanical and mechano-electric interactions in cardiac tissue. At the cellular level, the electro-mechanical coupling (ECC) and mechano-electric feedback (MEF) between the membrane action potential (AP) generation and cellular contraction are provided by the mechano-dependence of intracellular calcium kinetics. Mechanisms of cooperativity in kinetics of regulatory calcium-troponin complexes and force-generating acto-myosin cross-bridges underlie this mechano-dependence. At the tissue level, electrical waves of depolarization and repolarization and mechanical wave of deformation arising due to the electrical and mechanical coupling between cardiomyocytes also affect each other. ECC and MEF mechanisms in the heart on the cellular level are widely discussed [4], but influence of the mechanical interactions between cells on properties of

the electrical wave in myocardium remains largely under appreciated.

The model of myocardium sample is described in the work [5].

To focus on the basic mechanisms affecting MEF, this study is based on both simple geometry and fibers orientation. We considered a tissue geometry of dimension $20 \text{ mm} \times 10 \text{ mm} \times 10 \text{ mm}$. The model accounts for the electrical and mechanical anisotropy of the myocardial tissue associated with the orientation of the muscle fibers. The fibers were modeled unidirectional along the long axis as visualized in Figure 1. We started here with the tissue consisting of cardiomyocytes with identical electrical and mechanical properties. In this case we evaluate effects of the initial electrical asynchrony induced by the excitation wave propagation on the tissue performance.

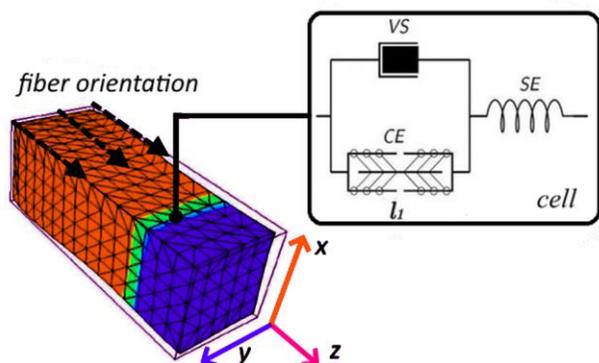


Figure 1. The scheme of myocardium sample. The rheological scheme shows mechanical structure of single virtual cardiomyocyte corresponding to a cell from the tissue, where the contractile element (*CE*) is connected in series to the passive elastic element (*SE*) and in-parallel to the viscous element (*VS*). l_i is deformation of *CE* relative to its slack length.

3. Results

We simulated two modes of contraction: isometric [6] and isotonic. Isometric contractions are widely used in experimental cardiac physiology to mimic isovolumetric contraction of the intact ventricle in isolated myocardium preparations (trabeculae or papillary muscles). Isotonic mode of contractions is widely used in experiments on isolated cardiac samples to study load-dependence of cardiac mechanical function. Here a constant afterload is applied on the muscle, which can cyclically shorten and lengthen under this load when excited.

Both panels of the Figure 2 show heterogeneous electromechanical behavior of the cells in the process of their mechanical and electrical interactions in isotonic mode of contraction.

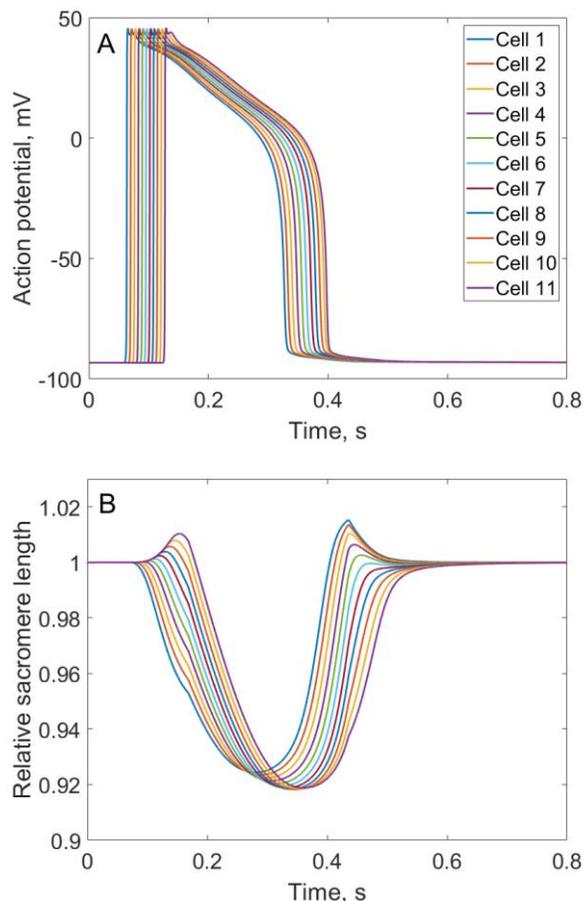


Figure 2. Isotonic mode of contraction. (A) Action potentials and their duration (APD) for various cells along the axis z . (B) deformations for various cells along the axis z in the electromechanical simulation (the cells were selected with a step of 0.2 mm from a middle fiber of myocardium sample).

The mechanical interactions between coupled cells are due to their asynchronous excitation during the electrical wave propagation. They reveal dynamic changes in the cell lengths through the tissue in isometric phase of contractions. Here, earlier activated contracting cardiomyocytes from the left part of the tissue sample pre-stretch passive right cells until the excitation wave reaches them. When the whole tissue is activated, the field of deformation depends on the mechanical activity of every interacting cell.

Figure 3 demonstrates the gradients in action potential duration (APD) developed in cardiomyocytes along the one fiber in tissue. In isometric mode of contraction, we observe a gradual APD shortening along the fiber down to the values less than APD in isolated cardiomyocyte at the right fiber end.

In isotonic mode of contraction in accordance with experimental data APD in cell increase with decrease in afterload. Moreover, we found that quantitative APD

increment depended on the cell position within the tissue. Surprisingly, the greater change in APD was observed in the later activated cardiomyocytes in the fiber, so the APD distribution along the fiber became more homogeneous during low-loaded contractions as compared to heavy-loaded isometric twitch.

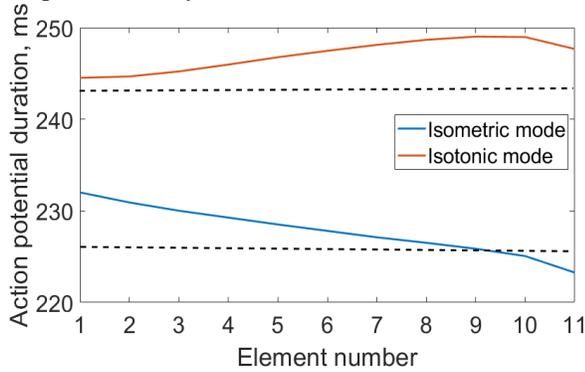


Figure 3. Action potentials duration (APD) for various cells of one fiber along the axis z for Isometric (blue line), afterloaded twitches (red line) and isolated cardiomyocyte (dashed lines).

This effect can be explained within the framework of the model. The lower the applied load the shorter is the isometric phase of afterloaded contraction where cardiomyocytes actually interact and influence each other, thus their electro-mechanical behavior becomes more uniform.

Figure 4 demonstrates isometric and isotonic contraction simulated in the model of myocardium sample.

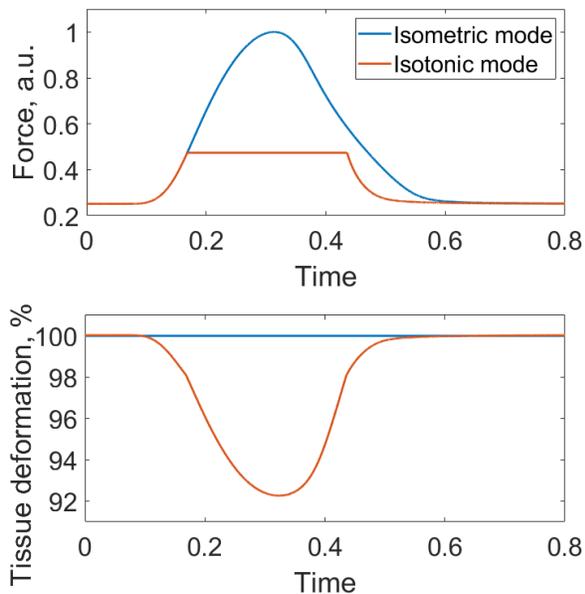


Figure 4. Isometric (blue lines) and afterloaded twitches (red lines) of a tissue under the 50% load from isometric force. Force generated by the tissue (top) is shown against corresponding tissue shortening (bottom).

Analysis of the intracellular activity in our tissue model allowed us to investigate in detail the effects of interplay between the electrical and mechanical coupling on the force and cell shortening, as well as on the other intracellular characteristics of excitation and contraction in the cardiac tissue.

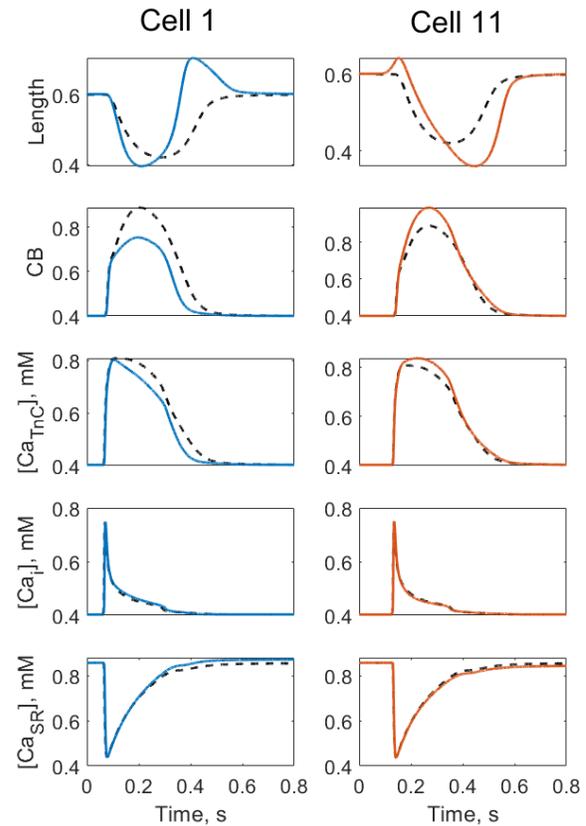


Figure 5. The influence of the mechanical interaction on mechanical activity and Ca^{2+} kinetics in the left-end 1 (left) and the right-end cell 11 (right) in the model of myocardium sample (solid lines) compared to isolated cardiomyocyte (dashed lines) in isometric mode of contraction. From top to bottom: deformations of cell, the number of force-generated cross-bridges N , $[Ca_{TnC}]_i$, $[Ca^{2+}]_i$, and SR Ca^{2+} concentration.

Figure 5 compares an activity of two cells from the left and right (Cell 11, red lines) ends of the middle fiber of myocardium sample in isometric contraction with the activity of the same cells in isolation.

Note, that in the model electrical excitation wave spreads throughout the tissue from left-to-right, so left-side cells are activated earlier than right-side cells. Owing to the passive stretching of the later activated right-end cell its excitation and further contraction started at a larger initial length than that in the earlier activated left-end cell.

Let us first consider the performance of the earlier activated left-end cell 1. The greater velocity and the peak

shortening of the sarcomeres in the first cell in fiber to a decrease in the number of force-generating cross-bridges (CB). This, via the cooperative mechanisms, increases the rate constant of Ca^{2+} dissociation from the CaTnC complexes, decreasing the concentration of Ca^{2+} bound to troponin C during the contractile cycle and thereby increasing the concentration of the free Ca^{2+} in the cytosol. Such a small surplus in $[\text{Ca}^{2+}]_i$ during the myocyte contraction provides an additional Ca^{2+} uptake to the sarcoplasmic reticulum (SR), which results in additional cycle-by-cycle Ca^{2+} accumulation in the SR.

The behavior of the right-end cell 11 activated last in the fiber during the electrical wave propagation “mirrors” the events that occurred in the left-end cell 1.

Such intracellular mechanisms of the mechano-electric coupling in the cardiac tissue allowed to produce mechano-dependent gradients of intracellular Ca^{2+} level in the cells. This Ca^{2+} load gradients were correlated with the gradients of APD.

Based on all discussed results we may speculate that an inherent heterogeneity between cardiomyocytes existing in the intact heart, especially recognized in different transmural layers of ventricles, may be considered as one of evolutionary mechanisms to reduce the dynamical heterogeneity arising due to the cell electro-mechanical interaction against the background of their inevitably asynchronous stimulation.

4. Conclusion

In the framework of the model of homogeneous myocardium sample, we have shown that interaction of cardiomyocytes in cardiac tissue arising due to electrical and mechanical asynchrony greatly affects electro-mechanical activity of both single cardiomyocytes and the total tissue. It was shown that electro-mechanical activity of the tissue is significantly modulated by external (afterload) and internal (amplitude of local deformations) mechanical conditions. Due to fine tuning (autoregulation) of properties of each cardiomyocytes under changing conditions the originally homogeneous tissue becomes heterogeneous one.

The influence of mechanical conditions on AP generation in cells and repolarization wave spread is resulted from MEF mechanisms, including cooperative mechanisms of Ca^{2+} activation of sarcomere actin filaments.

In the future, we plan to simulate the myocardium tissue with different fiber orientations and initial stimulation regions and take into account transmural nonuniformity of cardiomyocytes inherent to the LV wall.

Acknowledgments

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Address for correspondence:

Name. Alexander Kursanov

Full postal address. IIF UrB RAS, 620049 Pervomayskaya 106, Yekaterinburg, Russia

E-mail address. alexander.kursanov@gmail.com