Role of Mechanics in Rhythm Disturbances in 1D Mathematical Model of Myocardial Tissue with Local Ca^{2+}-Overload

Alexander Kursanov[1,2], Olga Solovyova[1,2,3], Leonid Katsnelson[1,2], Vladimir S. Markhasin[1,2]

[1]Ural Federal University, Yekaterinburg, Russia
[2]Institute of Immunology and Physiology UB of RAS
[3]Institute of Mathematics and Mechanics UB of RAS

Abstract

Possible contribution of the mechanics to the arrhythmogenesis in Ca^{2+} overloaded cardiomyocytes has been under appreciated. Earlier developed mathematical model of cardiomyocyte electromechanical function predicted a significant role of intra- and extracellular mechanical factors in triggering rhythm abnormalities.

We utilized the cellular model to study effects of the electromechanical coupling between cardiomyocytes in a 1D heterogeneous muscle strand comprised normal (N) and sub-critical (SC) cardiomyocytes with moderately decreased Na^+-K^+ pump activity. The single SC cardiomyocytes did not demonstrate spontaneous activity during isometric contractions at a reference length.

In the tissue, excitation spreads via electro-diffusional cell coupling and activates cell contractions and force development. Mechanical interactions between N- and SC-cells in the tissue resulted in the spontaneous activity emerged in the SC zone between the regular stimuli. The results suggest that ectopic activity may emerge in a rather small SC-region and expand by capturing normal regions in myocardium due to the electromechanical coupling between cardiomyocytes.

1. Introduction

It is well-known that Ca^{2+} overload may cause cardiac arrhythmia. However, possible contribution of the mechanical factors to the arrhythmia onset in Ca^{2+}-overloaded cardiomyocytes has not been sufficiently investigated.

Utilizing our cellular Ekaterinburg-Oxford (EO) model of the electro-mechanical activity in cardiomyocytes, we have predicted that mechanical factors may play a significant role in arrhythmogenesis [1, 2]. Ca^{2+} overload in the cellular model was induced by various levels of reduction in Na^+-K^+ pump activity [1]. Severe Ca^{2+}-overload in cells with strongly decreased Na^+-K^+ pump activity ($K_{m,Na}$ raised to 165% of normal, causing intracellular Na^+ accumulation, followed by Ca^{2+} overload) led to spontaneous Ca^{2+} releases from the SR with subsequent electrical activation of the cell, similar to earlier modelling-based observations on spontaneous SR Ca^{2+} release as a possible contributor to ischemic arrhythmogenesis [3]. These 'ectopic' AP aroused independently of the mechanical conditions of the cell contractions. In cardiomyocytes with less severe reduction of Na^+-K^+ pump activity, emergence of spontaneous activity was mechano-dependent. In particular, reductions in the mechanical pre- or after-load gave rise to AP generation in the pathologically disturbed cells [1]. These model predictions were experimentally verified [2].

The results suggested that ectopic activity in pathological foci and border zone tissue can be promoted by their mechanical interactions with normal or less severely affected myocardium [1]. Here, we try to assess this hypothesis in a 1D myocardial tissue model, composed of electrically and mechanically coupled cardiomyocytes with varying Ca^{2+}-contents, from normal to severe Ca^{2+}-overload, with region of different relative size occupied by the disturbed cells within the whole myocardial strand.

2. Methods

2.1. 1D model of myocardial tissue

Recently we developed a continuous 1D mathematical model of myocardial tissue, as a muscle strand formed of mechanically *and* electrically interacting cardiomyocytes [4]. Any cardiomyocyte in the model is considered as a functional point of myocardial tissue, which forms a continuous 1D medium. Each cardiomyocyte in the 1D tissue model has its own local, dynamically changing shape and mechanical environment within the tissue during the contractile cycle. As in native tissue, the electrical wave of excitation propagates along a dynamically deformable medium. Our 1D model accounts

for both micro- and macro-circuits of the electro-mechanical and mechano-electric interactions in the heart tissue. Each cell is described by our EO-model of cellular electro-mechanics, excitation propagation is governed by a reaction-diffusion equation, and macro-mechanics at each point is defined accounting for integrated cellular mechanics along the entire fibre.

Here we consider isometric contractions of 1D myocardial strands combining normal cells with regions of Ca^{2+} overloaded cells (see below).

2.2. Simulation of cellular Ca^{2+} overload

Cellular Ca^{2+} overload in the model is simulated by a reduction of Na^+-K^+ pump activity via increasing sodium Michaelis constant $K_{m,Na}$ for Na^+-K^+ pump current (i_{NKP}).

As in real cells, a decrease in i_{NKP} in the model produces a gradual accumulation of intracellular Na^+ that accelerates Na^+-Ca^{2+} exchange which leads to beat-to-beat increase in intracellular Ca^{2+} stored in the SR of the virtual cardiomyocyte.

Following our previous findings [1], we used here essentially distinct cellular samples with different degrees of Na^+-K^+ pump reduction as compared with normal cells (N-cells, $K_{m,Na}$ < 37 mM). Table 1 summarizes characteristics of the activity of a N-cell ($K_{m,Na}$ = 24,2 mM) during steady state isometric twitches at an initial sarcomere length of 2.1 μm with pacing rate of 1 Hz.

Table 1. Characteristics of the activity in single N- and SC-cells and corresponding strands in isometric twitches.

	N-sample	SC-sample	N-strand	SC-strand
APD (ms)	200	105	210–185	112–90
$[Ca^{2+}]_{SR}$ (μM)	0,88	0,96	1,05–0,7	1,1–0,96
PF (mN)	9,2	9,8	8,8	8,7±0,4
TPF (ms)	210	202	215	198
T_{30} (ms)	170	190	175	188

$[Ca^{2+}]_{SR}$ - diastolic Ca^{2+} load in the SR, APD – action potential duration, PF – peak active force, TPF – time to PF, T_{30} – relaxation time to 30% of PF. In the strands, ranges of cellular values are shown. Mean PF ± SD is shown for the SC-strand, see text below and Fig. 2 left.

Figure 1 illustrates an extrasystolic attack developed in a pathological cell (P-cell, $K_{m,Na}$ = 45 mM) with rather strong Na^+-K^+ pump reduction ($K_{m,Na}$ ≥ 40 mM) in isometric twitches under the control conditions. Such disturbances emerge in P-cells independently of the pacing rate and the mechanical conditions of contraction, but essentially involving cooperative mechanisms of myofilament Ca^{2+} activation (see our earlier work [1]).

Sub-critical cells (SC-cells) represent a border-zone between the N- and P-cells with $K_{m,Na}$ from a narrow range of 37–40 mM. In SC-cells, emergence of spontaneous activity is sensitive to the pacing rate and mechanical conditions of cell contraction. A single SC-cell in Figure 1 produces stable isometric contractions under the same preload and pacing rate as applied to the N- and P-cells (Fig. 1, see also Table 1 for the details). Note, that the peak force developed by the SC-cell is slightly higher than that of N-cells, as the SC-cell is more loaded with Ca^{2+} due to moderately reduced Na^+-K^+ pump activity. However, a reduction in either mechanical preload (a decrease in the initial sarcomere length) or after-load (switch from heavy-loaded isometric to low-loaded isotonic contractions) gives rise to extra AP generation in the cell [1].

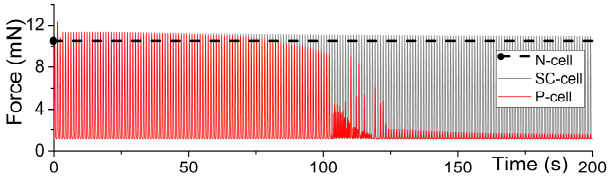

Figure 1. Beat-to-beat transient of the peak force developed by single SC-, and P-cells in isometric twitches at control conditions. P-cell undergoes an episode of extrasystolic activity which ends up with crucial reduction of peak force developed by the cell.

3. Results

1D models combining N-cell tissue with regions of either SC- or P-cells were used to simulate isometric contractions of strands with slack length L_0 of 20 mm, pre-stretched under preload up to the initial length L = 24.5 mm (22% stretch from L_0), providing initially uniform sarcomere extension to 2.1 μm throughout the tissue as that in single cell simulations (see above section). Initial values for phase variables in every cell of the 1D models were set as the diastolic steady state produced by the single N-cell model in isometric twitch under the control conditions. Then parameters $K_{m,Na}$ in the cells of disturbed region were set to either P- or SC-value. Excitation spread cell-to-cell throughout the tissue starting at either of the strand edges being paced (via a stimulating current) at 1Hz. Following beat-to-beat transients in the activity of the strand driven by cellular electrical and mechanical dynamic interactions were analyzed.

Most unpredictable results were obtained in 1D strands formed of N- and SC-regions, so we present them below in more details. Percentage size of the disturbed region varied from 100% to 10% of the strand length. Activity of a 1D model composed entirely of the N-cells was used as a reference to compare with (see Table 1). Results obtained in combinations of N- and P- segments are also discussed shortly in the Discussion.

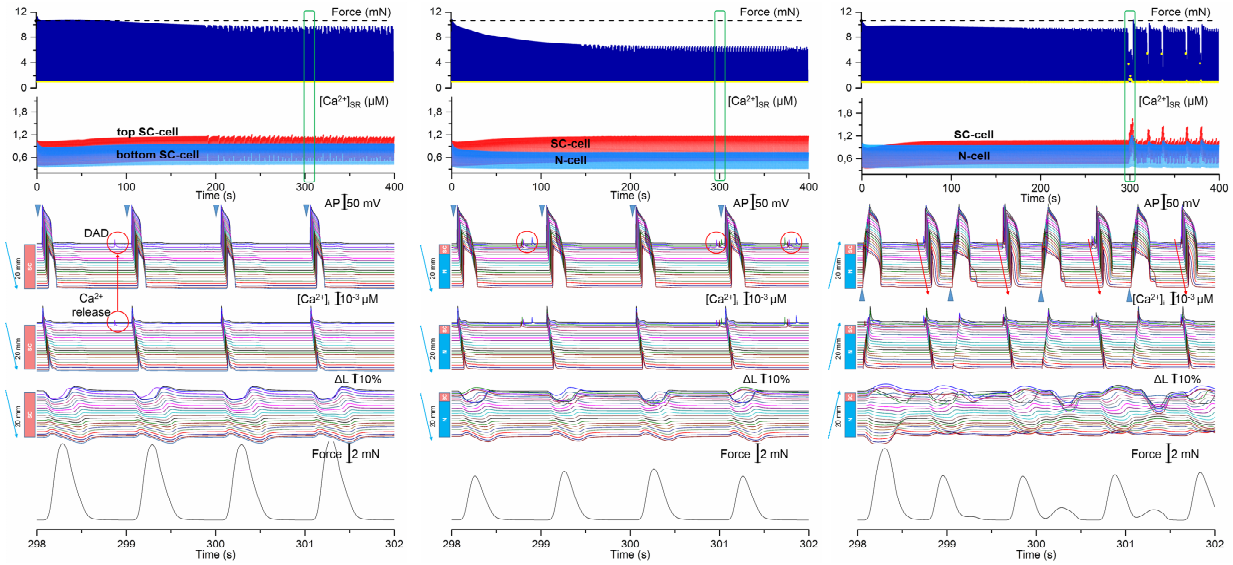

Figure 2. Delayed after-depolarizations (left and mid panels) and rhythm disturbances (right panel) arising in a 1D virtual tissue formed of 100% of SC-cells (left panel), 90% of N-cells and 10% of SC-cells (mid and right panels). Lines 3-5 show details on the simulated events corresponding to the time interval around 300 s from the cell coupling.

3.1. SC-cell coupling in 1D tissue

In a 1D tissue model composed of identical coupled SC-cells, a flat beat-to-beat decrease in the peak force lasted for about 200 cycles (200 s) then switching to quasi steady chaotic oscillations with a mean of about 6% lower than the reference force in the N-strand with a small coefficient of variation of 4.4% (see Fig. 2, left panel, Table 1).

Such mechanical disturbances in the SC-tissue resulted from spontaneous Ca^{2+} releases which appeared once in multiple beats in several cells of the strand during the late diastole prior to the regular stimuli. These premature Ca^{2+} releases induced sub-threshold membrane depolarizations or delayed after-depolarizations (DAD) in the SC-cells which also contributed to their disturbed activity and triggered force variations. Note, that DADs arose in the cells which were located closer to the paced edge of the SC-strand. These cells were activated earlier and underwent highest cyclic shortening during the regular twitches prior to the spontaneous Ca^{2+} releases (Fig. 2, left). Here the DADs in the earlier activated region of the SC-strand emerged after hundreds of cyclic deformations, that shifted the 'anyway present' Ca^{2+} accumulation (as a result of Na^{+}-K^{+} pump inhibition) beyond the threshold for spontaneous Ca^{2+} release from the SR.

Thus, moderate reduction of Na^{+}-K^{+} pump activity in the mechanically interacting SC-cells caused additional SR Ca^{2+} loading in the earlier activated SC-cells (see Table 1) which made them more vulnerable to spontaneous Ca^{2+} releases and DADs as compared with the single SC-cells and induced contractile instability in the tissue.

3.2. SC-regions in 1D tissue models

In a 1D strand composed of fifty-fifty SC- and N-cells and paced at either of the strand edge, the scenario of disturbances emerged was similar to that shown in Figure 2 (left panel), but surprisingly ending up with more essential force reduction (not shown). The strand paced at the SC-half end developed mean force of 66% of the reference force with rather high variations of 9.2%. Such an essential contractile failure in the fifty-fifty model resulted from more frequent spontaneous Ca^{2+} releases and DADs as compared with the SC-model which appeared in a larger number of cells from the SC-segment. Thus, the mechanical interactions between the N- and SC-segments in the heterogeneous strand more essentially disturbed activity in the SC-region, which made the entire tissue significantly less productive than either N- or SC-strand.

Unexpectedly, when the size of disturbed region was further reduced to 10% of the total strand length, the severity of electrical and contractile disturbances in the tissue rather increased and became essentially sensitive to the direction of the excitation wave. If the excitation spread from the SC- to N-region, the disturbances developed in the tissue were similar to that shown in the SC-strand (Figure 2, compare central with left panel), but closer to the fifty-fifty model, with about the same force reduction (mean force of 58% of ref. value with variations of 3.7%). However, premature Ca^{2+} releases and DADs were more frequent in the SC-region, and almost all the cells overcame the threshold Ca^{2+} loading

every 1-2 beats.

More complicated and severe disturbances were developed in the same 1D strand paced from the edge of N-region (Figure 2, right panel). Here, within about 300 beats after cell coupling, the virtual tissue developed bursts of extrasystolic activity. This spontaneous activity in the SC-zone arose between regular waves of excitation, and it was preceded by spontaneous Ca^{2+} releases, which induced either DADs, or extra-APs in SC-cells. Extra APs induced an ectopic focus, which spread retrogradely, invading the normal tissue. Note, that mechanical activity in the ectopic zone became very complicated and some SC-cells turned out into resisting and non-contracting tissue. In further muscle activity, multiple successive intervals of almost regular contractions (mean force of 92% of ref., variations of 3%) were interspersed by bursts extrasystoles.

Thus, even a little portion of the SC-cells producing frequent spontaneous Ca^{2+} releases and generating DADs and extra APs were able to trigger severe rhythm disturbances and acute contractile failure in the tissue.

4. Discussion

The most essential predictions derived from the model simulations suggest that sub-critically affected cardiomyocytes with rather moderate reduction of Na^+-K^+ pump activity and sub-threshold Ca^{2+} overload may develop an arrhythmogenic substrate in the tissue due to the mechanical interactions between the cells.

Earlier we have discussed in detail [1] mechanisms of such mechano-dependent facilitation of Ca^{2+} loading in shortening single cells due to length-dependent cooperative enhancement of Ca^{2+} dissociation from troponin C (TnC) with following increase in Ca^{2+} uptake by the SR. We showed that the cooperativity between myofilament activity and Ca^{2+} kinetics may essentially contribute to arrhythmogenesis in cardiomyocytes with sub-threshold Ca^{2+} overload.

In the 1D tissue model, the same mechano-dependent cooperativity of Ca^{2+} kinetics contributes to gradients in cellular functional characteristics, particularly gradients in APD and in the SR Ca^{2+} loading, evolved from the mechanical interactions between the cells (see Table 1). The gradients depend on the activation sequence of the tissue which governs nonuniform regional dynamical deformations modulating intracellular Ca^{2+} cycling, electrical activity and the SR content in the cells.

Of course, functional disturbances were found to be more severe in the tissue containing impaired P-cells which develop spontaneous activity independently of the mechanical environments. In this case ectopic P-cells provided for more of less frequent and long-lasting episodes of extrasystols independently of the activation sequence in the tissue (not shown). In more severe cases with almost block of Na^+-K^+ pump in P-cells (extremely high $K_{m,Na}$, e.g. $K_{m,Na}$=110 mM), their spontaneous activity may end up with complete conduction block in the P-region and total loss of contractility in the entire tissue (not shown).

Model simulations predict that the mechanical interactions between the cells via mechanisms of mechano-electrical coupling on both intra-cellular and inter-cellular levels may create a substrate for arrhythmia in heterogeneous tissue containing an area of Ca^{2+}-overloaded cells. Model analysis suggests that dependency of Ca-TnC binding kinetics on the force-generating cross-bridge concentration (a key co-operativity mechanism) plays an important role in triggering spontaneous activity in myocardial tissue, where local disturbances occur in pathological state.

The results suggest that ectopic activity may emerge in a rather small sub-critical myocardial region and expand by capturing normal regions in myocardium due to the electromechanical coupling between cardiomyocytes.

Acknowledgements

Development of the program code for 1D model of myocardium is supported by Programme of the Presidium of the Russian Academy of Sciences (II.4П #22) and effects of electro-mechanical coupling in myocardial tissue is supported by The Russian Science Foundation (#14-35-00005)

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Address for correspondence.

Kursanov Alexander (alexander.kursanov@gmail.com)
UrFU, 620002 Mira 19, Yekaterinburg, Russia