Mathematical modelling of mechano-electric feedback in cardiomyocytes

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Abstract — We earlier developed the mathematical model of electrical and mechanical activity in myocardium, which takes into account both direct coupling and feedback between excitation and contraction. In this paper, in the framework of the model we found conditions under which both the abrupt shortening and stretch of cardiac preparation can cause extra action potentials and hence anomalous deformations can be arrhythmia sources. In the framework of the model, we establish possible mechanisms underlying the Anrep phenomenon that reflects a relationship between myocardium contraction and vascular resistance in the intact heart.

In the classical scheme of excitation-contraction coupling in cardiomyocyte, the intracellular Ca$^{2+}$ kinetics is the most important link providing a direct coupling between electric cell activity and a contractile act. This coupling is mainly realized by two potential-dependent currents transferring Ca$^{2+}$ ions via the cell membrane. The first current, an inward Ca$^{2+}$ current via L-type channels, $i_{Ca,L}$, which is activated by membrane depolarization, triggers Ca$^{2+}$ release from sarcoplasmic reticulum, which is necessary for the activation of contractile proteins [2].

Besides, a Ca$^{2+}$ influx into a cell, together with $i_{Ca,L}$, provides the maintenance of a certain amount of Ca$^{2+}$ in a cell. The second current, an electrogeneous Na$^{+}$–Ca$^{2+}$ exchange current, $i_{NCX}$, transfers Ca$^{2+}$ ions via the membrane into a cell (reverse mode) or outward (forward mode) due to exchange with Na$^{+}$ ions. The current $i_{NCX}$ participates to a certain degree in increasing the free calcium concentration in cytosol, [Ca$^{2+}$]i, in the contraction process and also provides the Ca$^{2+}$ extrusion from a cell in the relaxation process sustaining Ca$^{2+}$ homeostasis in a cell [2]. Moreover, the above two currents play an important role in the regulation of the form and duration of the action potential (AP), i.e. specific change in the membrane potential during a contractile cycle.

In the classical scheme of excitation-contraction coupling the effect of mechanical conditions for cardiomyocyte contraction on the excitation process was not taken into account. However, it was shown, for example, in experiments on solitary car-
Cardiomyocytes and multicellular heart preparations that the duration of the AP (APD) substantially varies with the initial length of the preparation or load during contraction [16, 17, 28, 29]. This data and a great deal of other experimental and clinical data testify that there is mechano-electric feedback in the regulation of a cardiomyocyte function (see [3, 14, 18] for review). By now there are two key mechanisms of mechano-electric feedback at the cellular level: (i) the activation of ionic currents via mechanosensitive channels; (ii) the effect of the mechanosensitive Ca²⁺ kinetics on calcium-dependent currents. The interrelation between these mechanisms and their relative contribution to the contraction-excitation coupling have remained unclear so far.

Since numerous intracellular processes participating in electro-mechanical coupling and feedback are closely connected and mutually affect one another, search for mechanisms of mechano-electric feedback in physiological experiments is extremely difficult. Therefore the mathematical models are unique tools for explaining the causal links between the mechanical and electrical processes in cardiomyocytes [7, 21, 23, 25]. We developed the mathematical model of electrical and mechanical activity of cardiomyocytes (see Section 1) and suggested a method for assessing the contribution of various intracellular mechanisms to the AP response to mechanical perturbations (see Section 2). In the framework of this model a number of experimentally registered effects of the influence of the muscle length and load during contraction on the form and duration of the AP, which are generated by cardiac cells, were reproduced [25]. In the present paper, using the model, we analysed the effect of transient forced deformations (stretch or shortening) of myocardium on its electric function (Subsections 3.1, 3.2). We further give examples of deformations caused by extra perturbations of cardiac cells (Subsection 3.3), which could be a source of occurrence of arrhythmias in an intact tissue. In the framework of the model we also consider prolonged transitions proceeding in myocardium in response to the change in the mechanical conditions (Section 4).

1. MATHEMATICAL MODEL OF ELECTRICAL AND MECHANICAL ACTIVITY IN HEART MUSCLE

We have developed the mathematical model of electromechanical coupling in heart muscle [25]. The model describes the generation of the AP created by ionic currents via a sarcolemma, as well as Ca²⁺, Na⁺, K⁺ ion kinetics in cardiomyocytes. Along with electrochemical processes, the model describes the time variation in length and force, which are generated by sarcomeres and the muscle as a whole. Let us briefly describe this model.

The description of electric activity is borrowed from the well-verified model developed by Noble et al. [22], which is widely used by electrophysiologists.

The rate of change of the membrane potential $E$ is defined by the sum of ionic currents $i_k$:

$$\frac{dE}{dt} = -\frac{1}{C_m} \sum_k i_k$$

(1.1)
where $C_m$ is the membrane capacity.

The value of the current $i_k$ transferring ions $X$ via the specific membrane channels is determined by the difference between the membrane potential $E$ and the equilibrium electrochemical potential $E_X$ for ions $X$:

$$i_k = g_k(E - E_X) \tag{1.2}$$

where $g_k$ is conductance of channels for ions $X$. Note that in electrophysiology the current is commonly taken to be positive, $i_k > 0$, if it induces a flux of positive charges from a cell outward and vice versa.

The equilibrium potential $E_X$ such that the electromotive force is balanced by the ion concentration difference gradient is described by the classical Nernst equation:

$$E_X = \frac{RT}{zF} \ln \left( \frac{[X]_{\text{out}}}{[X]_{\text{in}}} \right) \tag{1.3}$$

where $R$ is the gas constant, $T$ is the absolute temperature, $F$ is the Faraday number, $z$ is the ion valence, $[X]_{\text{out}}$ and $[X]_{\text{in}}$ are ion concentrations of a given kind outside and inside a cell.

The conductance of the ion channels $g_k$, as a rule, depends in a complicated way on the potential $E$, the concentrations $[X]_{\text{out}}$ and $[X]_{\text{in}}$, and on the probability $P_k$ for the channels to be in an open state, which can vary with time, i.e. $g_k = g_k(E, [X]_{\text{in}}, [X]_{\text{out}}, P_k)$.

For example, in our model the value of a fast inward current via the sodium channels $i_{Na}$ is defined by the relation

$$i_{Na} = P_{Na} \bar{g}_{Na}(E - E_{Na}), \quad P_{Na} = m^3 h. \tag{1.4}$$

Here $\bar{g}_{Na}$ is the peak conductance and $P_{Na}$ is the probability of opening of the channels. The channel opening is supposed to be possible only for a certain combination of the state of three ‘activating’ and one ‘inactivating’ control particles. The probability of this combination is $R_{Na} = m^3 h$, where $m$ and $h$ are the probabilities for the corresponding particles to be in the state favourable for the channel opening. The change in the probabilities $m$ and $h$ is described by the conventional kinetic equation of the form

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m, \quad \frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \tag{1.5}$$

where the parameters $\alpha_m, \beta_m, \alpha_h, \beta_h$ depend on $E, [X]_{\text{out}}$, and $[X]_{\text{in}}$.

In particular, the model takes into account the currents via the mechanosensitive channels $i_{MSC}$ [26] that are directly activated by mechanical perturbations, for example, the heart preparation stretch [15]:

$$i_{MSC} = g_{MSC}(E - E_{MSC})/(1 + K_{MSC}e^{-\gamma_{MSC} \Delta L}) \tag{1.6}$$
where \( E_{\text{MSC}} \) is the reversion potential for \( \kappa_{\text{MSC}} \). \( g_{\text{MSC}} \) is the peak conductivity for mechanosensitive membrane channels, \( \Delta L \) is the deviation in the current preparation length from some fixed length, \( K_{\text{MSC}} \) and \( \gamma_{\text{MSC}} \) are the parameters defining the ‘length dependence’ of the current.

Along with the ion transport over the concentration gradient via the membrane channels, there are also cell currents that are induced by molecular pumps translocating ions against concentration gradients. The active ion transport is possible due to either exchange with other ions (for example, Na\(^+\)–Ca\(^{2+}\) exchange current) or the energy consumption of ATP (for example, Na\(^+\) and K\(^+\) currents via Na\(^+\)–K\(^+\) ATPase). In order to describe the active ion transport in the model, we use quasi-stationary equations for interaction between ions and proteins, their conformation changes provide ion translocation via the membrane. For example, the expression for Na\(^+\)–Ca\(^{2+}\) exchange current \( i_{\text{NCX}} \) capable of changing the polarity and translocating 3Na\(^+\) against 1Ca\(^{2+}\) has the form

\[
i_{\text{NCX}} = \frac{e^{2\gamma_{\text{NCX}} F} [\text{Na}\(^{+}\)]_{\text{out}}^3 [\text{Ca}\(^{2+}\)]_{\text{in}} - e^{-2(1-\gamma_{\text{NCX}}) F} [\text{Na}\(^{+}\)]_{\text{in}}^3 [\text{Ca}\(^{2+}\)]_{\text{out}}}{1 + [\text{Ca}\(^{2+}\)]_{\text{in}} / K_{\text{NCX}}} \tag{1.7}
\]

where \( k_{\text{NCX}} \) is a parameter defining the exchange current amplitude and the parameters \( K_{\text{NCX}} \) and \( \gamma_{\text{NCX}} \) define the exchange mechanism sensitivity to the change in Na\(^+\) and Ca\(^{2+}\) ion concentrations.

The \([\text{Ca}\(^{2+}\)]_{\text{out}}\), \([\text{Na}\(^{+}\)]_{\text{out}}\), and \([\text{K}\(^{+}\)]_{\text{out}}\) concentrations are assumed to be constant. At the same time, the transmembrane ion fluxes result in a substantial change in \([\text{Na}\(^{+}\)]_{\text{in}}\), \([\text{K}\(^{+}\)]_{\text{out}}\), and especially \([\text{Ca}\(^{2+}\)]_{\text{in}}\) concentrations. The change in the \([\text{Ca}\(^{2+}\)]_{\text{in}}\) concentration in a cell also essentially depends on intracellular processes, in particular, on interaction between Ca\(^{2+}\) ions and intracellular ligands \( L \) and on exchange with intracellular Ca\(^{2+}\) sources. The change in the above concentrations is described by the equations:

\[
\begin{align*}
\frac{d[\text{Ca}^{2+}]_{\text{in}}}{dt} & = \sum_{k_1} F_{k_1,\text{Ca}^{2+}} + \sum_{l} \frac{d[\text{Ca} - L]}{dt} + F_{\text{SR,rel}} - F_{\text{SR,pump}} \\
\frac{d[\text{Na}^{+}]_{\text{in}}}{dt} & = \sum_{k_2} F_{k_2,\text{Na}^{+}}, \quad \frac{d[\text{K}^{+}]_{\text{out}}}{dt} = \sum_{k_3} F_{k_3,\text{K}^{+}} - D_{\text{K}^{+}}.
\end{align*}
\tag{1.8}
\]

Here \( F_{k,X} = \pm |i_k| / (V_{\text{cyt}} F) \) is the transmembrane ion flux \( X \) with current \( i_k \), where the sign of flux is defined by the direction of ion motion, \( V_{\text{cyt}} \) is the cytosol volume; \([\text{Ca} - L]\) is the concentration of Ca\(^{2+}\) complexes with intracellular ligands; \( F_{\text{SR,rel}} \) and \( F_{\text{SR,pump}} \) are Ca\(^{2+}\) fluxes between intracellular compartments (see below); \( D_{\text{K}^{+}} \) is K\(^+\) diffusion in an extracellular medium.

The constant membrane potential at rest, which is called a resting potential, is defined by a number of differently directed background currents via the channels and exchangers sustaining cellular homeostasis. The resting potential is close to the equilibrium K\(^+\) potential \( E_K = -94.5 \text{ mV} \) because the membrane permeability at rest for other ions is low.
During the cardiac cell excitation (due to a stimulating signal from the conducting system of the heart or the artificial electrical stimulation of heart preparation in a physiological experiment) the membrane potential increases to a threshold level and thus the ion channels and the exchangers become activated. In the model, the prethreshold perturbation of the membrane potential, which initiates the cell excitation, is prescribed by the short-time stimulating depolarizing current \( i_{stim} < 0 \). Ionic currents that occur after threshold depolarization provide the characteristic cyclic change in the membrane potential, which is called an action potential. In particular, the fast sodium current via Na\(^+\) channels, \( i_Na \), is responsible for fast upstroke. The slow inward calcium current via L-channels, \( i_{CaL} \), mostly provides the phase of AP plateau. Outward currents via K\(^+\) channels, viz. delayed outward K\(^+\) current, \( i_K \), and the inward rectifier K\(^+\) current, \( i_{K1} \), define the membrane repolarization up to the resting potential level. The above currents, \( i_{NCX} \) and \( i_{MSC} \), also substantially affect the AP configuration.

**Model description of the mechanical activity of heart muscle** is based on the classical three-element scheme of a contraction unit, which consists of a contractile element (CE) or sarcomere as well as associated serial (SE) and parallel (PE) elastic elements. According to the above scheme the muscle length, \( L \), is taken to be proportional to the parallel element length, whereas the tension \( T \) produced by the muscle is proportional to the sum of tensions in elastic elements \( T_{SE} + T_{PE} \).

In the framework of the model, we describe dynamic changes in the muscle length \( L \) and the tension \( T \) under various contraction conditions. For example, the model can generate either the change in the tension \( T \), given the change in the muscle length \( L = \varphi(t) \) (in particular, in the isometric regime at the fixed length \( L \equiv \text{const} \)), or the change in the length \( L \), given the change in the load \( T = \psi(t) \) (for example, in the isotonic regime at the fixed load \( T \equiv \text{const} \)).

Suppose \( l_1 \) is the CE deformation, i.e. the deviation in the sarcomere length from the resting length in the process of contraction (relaxation), \( b \) is the PE deformation. These two variables are basic phase variables in the mechanical model block.

It is obvious that the SE deformation is equal to the difference between the PE and CE deformations, i.e. to \( l_2 - l_1 \). The deformation-tension coupling for elastic elements is prescribed by the experimental data in the form of the parametric functions:

\[
T_{SE} = T_{SE}(l_2 - l_1), \quad T_{PE} = T_{PE}(l_2).  \tag{1.9}
\]

The force \( T_{CE} \) generated by sarcomere is due to interaction between crossbridges of myosin molecules and the active centers of actin molecules and depends on the sarcomere length and the velocity of its shortening/lengthening in the model, as well as the calcium activation process of fine filaments.

It is logical to put

\[
T_{CE} = \lambda f N.  \tag{1.10}
\]

Here \( f \) is the force generated by an averaged force-generating bridge, \( N \) is the fraction of force-generating bridges per sarcomere, \( \lambda \) is a proportionality coefficient.

It is assumed that \( f \) depends on the shortening/lengthening velocity of sarcomere \( v = dl_1/dt \), i.e. \( f = f(v) \). The function \( f(v) \) is given in explicit form (by the
experimental data) and allows us to find the velocity \( f \) in explicit form, given the bridge load \( v = v(f) \). In view of this and the fact that the tensions of the series-connected sarcomere CE and the elastic element SE are equal, \( T_{CE} = T_{SE} \), we derive from (1.9)–(1.10) the equation for \( l_1 \):

\[
\frac{dl_1}{dt} = v \left( \frac{T_{SE}(l_2 - l_1)}{\lambda N} \right).
\]

(1.11)

The kinetics of the force-generating bridges is described by the equation:

\[
\frac{dN}{dt} = k_+ \left( l_1, \frac{dl_1}{dt}, [Ca - TnC] \right)(1 - N) - k_\text{off} N.
\]

(1.12)

The rate of attachment of the bridges to actin depends on the sarcomere length (i.e. on \( l_1 \)), the velocity of its shortening or stretch, \( \frac{dl_1}{dt} \), and on the average concentration of calcium complexes with regulator protein-specific troponin C, \([Ca-TnC]\).

The change in \([Ca-TnC]\) is described by the kinetic equation:

\[
\frac{d[Ca - TnC]}{dt} = k_{on}(TnC_{tot} - [Ca - TnC])[Ca^{2+}]_{in} - k_{off}(N,[Ca - TnC])[Ca - TnC].
\]

(1.13)

One of the most important features of our model is that it takes into account in equations (1.12)–(1.13) the cooperative mechanisms in the process of calcium activation of contractile proteins, which are found experimentally earlier [4 – 6]. The probability of binding the bridges cooperatively increases due to conformational transformations of regulator actin proteins, which are caused by the formation of calcium complexes with troponin C. This mechanism is formalized as a power dependence of the rate of binding the bridges \( k_+ \) on the value of \([Ca-TnC]\) [see equation (1.12)]. On the other hand, the affinity of troponin for calcium increases, first, as the concentration of strongly bound crossbridges, \( N \), increases and, second, with increasing \([Ca-TnC]\). These links are formalized as a decreasing dependence of the constant of the decay rate \( k_{off} \) on the values of \( N \) and \([Ca-TnC]\) [see equation (1.13)].

Taking into account the above mechanisms in the model allowed us to reproduce and explain quite a number of sophisticated mechanical and mechanochemical phenomena observed in the active myocardium [9, 12, 25, 27].

Finally, the final equation in the mechanical model block is the equation for finding \( l_2 \). Given the change in the muscle length, \( l_2 \) is specified in the explicit form:

\( l_2 = \varphi(t) \). For example, \( l_2 \equiv \text{const} \) in the isometric regime. Given the change in the muscle load, \( l_2 \) is found from the identity \( T_{SE}(l_2 - l_1) + T_{PE}(l_2) = \psi(t) \). For example, we can write the equation for \( l_2 \):

\[
\frac{dl_2}{dt} = \begin{cases} \varphi / (\psi - (T_{SE})_{l_1} \frac{dl_1}{dt} / (T_{SE} + T_{PE})_{l_2} ) & \text{if length control} \\ \frac{dl_1}{dt} & \text{if load control} \end{cases}
\]

(1.14)
The free intracellular calcium kinetics is a connecting link between electrical and mechanical activities of a cardiac cell because it is closely connected to transmembrane potential-dependent Ca\(^{2+}\) fluxes [see equation (1.8)] and directly included in the regulation of a contractile response of heart muscle [see equation (1.13)]. As mentioned above, exchange with intracellular structures, in particular, exchange with intracellular calcium sources, i.e. sarcoplasmic reticulum (SR) [the terms \(F_{\text{SR,rel}}\) and \(F_{\text{SR,pump}}\) in equation (1.8)] plays an important role in the \([\text{Ca}^{2+}]_{\text{in}}\) kinetics. An increase in \([\text{Ca}^{2+}]_{\text{in}}\) by an order of magnitude (from \(10^{-7}\)M in diastole to \(10^{-6}\)M in systole), which is needed for contractile cell activity during a cardiac cycle, is not mainly due to \(\text{Ca}^{2+}\) supply from the outside of a cell, but to calcium-induced release of calcium from SR [2]. The \(\text{Ca}^{2+}\) flux via the release channels on the SR membrane,

\[
F_{\text{SR,rel}} = \eta (i_{\text{CaL}}[\text{Ca}^{2+}]_{\text{JSR}})
\]  

(1.15)
depends in a complicated way on the current \(i_{\text{CaL}}\), which is a trigger of \(\text{Ca}^{2+}\) release from SR, and non-linearly depends on the calcium concentration in junctional SR, \([\text{Ca}^{2+}]_{\text{JSR}}\).

The process of the heart muscle relaxation is mainly due to the absorption of \(\text{Ca}^{2+}\) from cytosol back to SR by calcium pumps on the SR membrane. The \(\text{Ca}^{2+}\) flux produced by these pumps

\[
F_{\text{SR,pump}} = k_{\text{pump}} \frac{1}{1 + [\text{Ca}^{2+}]_{\text{NSR}}/K_{\text{pump}} [\text{Ca}^{2+}]_{\text{in}} + K_{\text{pump}}}
\]

(1.16)
depends on both \([\text{Ca}^{2+}]_{\text{in}}\) and the calcium concentration in net SR, \([\text{Ca}^{2+}]_{\text{NSR}}\). The parameter \(k_{\text{pump}}\) specifies the maximum absorption rate, \(K_{\text{pump}}\) is the affinity of pumps for \([\text{Ca}^{2+}]_{\text{in}}\), and \(K_{\text{NSR}}\) is the degree of the pump inhibition with increasing \([\text{Ca}^{2+}]_{\text{NSR}}\).

Finally, cytosol \(\text{Ca}^{2+}\) forms complexes with calcium-binding legands, in particular, with protein TnC [see equation (1.13)]. The \(\text{Ca}^{2+}\) consumption for the formation of these complexes is represented in equation (1.8) by the terms \(d[\text{Ca} - L_i]/dt\).

Thus, the model of mechanical and electrical phenomena in myocardium is the system of 27 ordinary differential equations. The electrophysiological model block comprises an equation for the membrane potential \(E\) [equation (1.1) with relations in the right-hand side of the form (1.2) or (1.7)] and an equation for dynamic parameters that specify the probabilities \(P_k\) for the ionic channels to be in an open state [the equations of the form (1.5)]. The mechanical model block supplements equations (1.11)–(1.14) for the deformations \(l_1, l_2\) the concentration of the force-generating bridges \(N\), and the control calcium complex with troponin C, \([\text{Ca–TnC}]\). The ‘chemical’ block of the system comprises the equations for \([\text{Ca}^{2+}]_{\text{in}}, [\text{Na}^{+}]_{\text{in}}, \)

\([\text{K}^{+}]_{\text{out}}\) [equations (1.8) with relations (1.15), (1.16) in the right-hand side], the equations for \([\text{Ca} - L_i]\) [analogous to equation (1.13)] and finally the equations for the \([\text{Ca}^{2+}]_{\text{JSR}}\) and \([\text{Ca}^{2+}]_{\text{NSR}}\) kinetics in the release and absorption compartments of SR.
In the framework of the described model we took into account both direct coupling and feedback between electrical and mechanical phenomena in cardiac cells. Indeed, due to the effect of the membrane potential on Ca\(^{2+}\) currents and hence on \([\text{Ca}^{2+}]_{\text{in}}\), the excitation contraction coupling is realized. On the other hand, the effect of the kinetics of the force-generating bridges on the \([\text{Ca–TnC}]\) kinetics and hence on \([\text{Ca}^{2+}]_{\text{in}}\) and the calcium-dependent currents ensures feedback between the contraction and electric activity of cardiomyocytes, which is called the mechanoelectric feedback. In addition to this mechanism, currents via the mechanosensitive channels [see (1.6)], which are directly activated by mechanical perturbations, can also contribute to the mechanically caused modulation of electric activity.

Most of the parameters in the model equations are taken from the experimental works, where these parameters were thoroughly determined. The other model parameters were chosen to achieve qualitative agreement between the model results and the values recorded in the physiological experiments.

The model system of ordinary differential equations belongs to the class of stiff systems. For the numerical integration, we first used the Runge-Kutta fourth-order method with a small step to obtain as the more exact numerical solution as possible. Then we compared the numerical solutions obtained by the Euler method with the obtained solution. We found the numerical integration step such that the two solutions are sufficiently close. We also used the combined explicit-implicit Euler method for the calculation of part of the variables explicitly and solved the system of algebraic equations for finding the other variables. This method allows us to increase the integration step as compared to that in the explicit method without loss of the solution quality. For the experiments with the model we developed a program that allows us to simulate various experimental conditions for muscle contraction, specify different initial conditions in the system, and change the free parameters.

The combined electromechanical model describes the mechanical and electrical behaviour of cardiomyocytes both in solitary isometric and isotonic contraction-relaxation cycles and in the series of contractions for various stimulation frequencies. The model successfully reproduces numerous effects that demonstrate the influence of the mechanical contraction conditions on the AP generation in cardiac cells. In particular, in the framework of the model we correctly reproduced both the effect of the muscle length on the APD in the isometric regime and the effect of the muscle load on the APD in the isotonic regime [25]. The inclusion of the mechanosensitive channels in the model allowed us to describe a number of phenomena that are irreproducible without considering the channels, for example, the repolarization crossover phenomenon after the cell stretch as compared to the control one [11, 29].

2. INTEGRALS OF DIFFERENCE CURRENTS

We developed the method for defining the relative contribution of various mechanisms of mechano-electric feedback to the change in the time dependence of the AP after the change in the mechanical contraction conditions [25]. The method is
based on the calculation of the integrals of difference in individual currents before and after a perturbation (difference current) and in the current time:

$$\Delta i_k(t) = i_{k,\text{test}}(t) - i_{k,\text{control}}(t).$$  \hspace{1cm} (2.1)$$

The sign of difference current (the sign ‘+’ is conventionally ascribed to a repolarization current transferring positive charges from a cell) indicates if the current alterations are repolarizing ($\Delta i_k > 0$) or depolarizing ones ($\Delta i_k < 0$) with respect to the control AP no matter where the control current $i_k$ was directed to: inside a cell (a depolarizing current) or outside it (a repolarizing current). In other words, $\Delta i_k > 0$ can imply either an increase in the control repolarizing current ($i_k > 0$) or a decrease in the absolute value of the depolarizing current ($i_k < 0$). The alteration of each current due to a test perturbation contributes to the dynamic change of the sum of the currents, which is responsible for the change in the membrane potential. Thus, the contribution of the alteration of each individual current to the total change in the potential can be assessed by the mathematical model.

The change in the membrane potential $\Delta E(t)$ in response to a perturbation is defined by the formula:

$$\Delta E(t) = E_{\text{test}}(t) - E_{\text{control}}(t) = \Delta E(t_0) + \left( -\frac{1}{C} \right) \sum_k \Delta Q_k(t)$$  \hspace{1cm} (2.2)$$

where $\Delta Q_k(t)$ is an additional charge transferred by the difference current $\Delta i_k(t)$. The relation holds for $\Delta Q_k(t)$:

$$\Delta Q_k(t) = \int_{t_0}^{t} \Delta i_k(\tau) \, d\tau.$$  \hspace{1cm} (2.3)$$

To assess the contribution of the additional charge transferred by the difference current $\Delta i_k(t)$ to the change in the membrane potential, we also calculate the increment of the potential $\Delta E_k(t)$ corresponding to this difference current:

$$\Delta E_k(t) = -\frac{1}{C} \Delta Q_k(t).$$  \hspace{1cm} (2.4)$$

A comparison of the time difference of $\Delta E_k(t)$ allows us to assess the contribution of each difference current to the change in the AP after a perturbation of the heart muscle.

### 3. EFFECT OF MECHANICAL PERTURBATIONS ON THE ELECTRICAL ACTIVITY IN HEART MUSCLE

#### 3.1. Effect of a transient release on the action potential

In the framework of the model we investigated the effect of ‘forced’ cyclic deformations of the ‘quick release-quick stretch’ heart muscle on the AP generation. In
the given series of the numerical experiments a prestretched virtual muscle in the control cycle contracted isometrically. In the test cycles the muscle was abruptly released at some instant thus allowing it to rapidly shorten to a given smaller length and then stretch back to the initial level at a short interval.

Figure 1 shows the results of modelling the AP response to the cyclic deformations in different phases of the control AP. The control isometric contraction and the corresponding AP were obtained with the virtual muscle length corresponding to the sarcomere length 2.23 µm. The length was abruptly decreased by 5% at various instants of the progressive control AP, kept at the new length for 20 ms, and then returned to its initial state. The following moments of deformation with respect to the control AP were considered: 1) the beginning of AP plateau (the moment of reaching 10% repolarization of AP<sub>10</sub>); 2) the middle of AP plateau (the moment of 20% repolarization of AP<sub>20</sub>); 3) the end of AP plateau (the moment of 30% repolarization of AP<sub>30</sub>); 4) the completion of repolarization (the moment of 99% repolarization of AP<sub>99</sub>).

As shown in Fig. 1a, the short-time shortening of the virtual muscle led to the inactivation of the muscle force-generation and additional depolarization. After a reverse stretch to the control length, the test AP gradually returned to the control AP only in the first case (curve 1 in Fig. 1), whereas under deformations 2 and 3 the test APs terminated later than the control AP (see curves 2, 3 in Fig. 1). The APD at the instant of reaching 90% of the repolarization level did not change under deformation at the beginning of plateau, increased by 6.6% (from 180 ms to 192 ms) under deformation in the middle of plateau, and increased by 12% (from 180 ms to 202 ms) under deformation at the end of AP plateau. Consequently, the closer was the moment of muscle release towards the end of AP plateau, the larger turned out to be the change in the APD. The change in the AP after the very last deformation 4 (see curve 4 in Fig. 1) was insignificant.

The results of modelling are in good agreement with the experimental data obtained on the papillary muscle of a cat [16, 17] and the ventricular strip of a frog [16].

Additional depolarization and AP prolongation in response to a quick muscle release in the phase of plateau is explained in the model by the mechano-dependent acceleration of Ca–TnC complexes decay. This leads to an increase in [Ca<sup>2+</sup>]<sub>in</sub> and, as a consequence, to the change in the time course of the current <i>i</i><sub>NCX</sub> via Na<sup>+</sup>–Ca<sup>2+</sup> exchanger (Fig. 1b). When the muscle releases in the phase of AP plateau, an increase in [Ca<sup>2+</sup>]<sub>in</sub> reduces the repolarizing component of the current <i>i</i><sub>NCX</sub> in the reverse-mode phase and under deformations closer to AP completion it increases the

<table>
<thead>
<tr>
<th>∆E(t) / mV</th>
<th>&lt;i&gt;i&lt;/i&gt;&lt;sub&gt;NCX&lt;/sub&gt;</th>
<th>&lt;i&gt;i&lt;/i&gt;&lt;sub&gt;Ca&lt;/sub&gt;</th>
<th>&lt;i&gt;i&lt;/i&gt;&lt;sub&gt;Ca&lt;/sub&gt;</th>
<th>&lt;i&gt;i&lt;/i&gt;&lt;sub&gt;K&lt;/sub&gt;</th>
<th>&lt;i&gt;i&lt;/i&gt;&lt;sub&gt;K&lt;/sub&gt;</th>
<th>&lt;i&gt;i&lt;/i&gt;&lt;sub&gt;pNa&lt;/sub&gt;</th>
<th>&lt;i&gt;i&lt;/i&gt;&lt;sub&gt;pNa&lt;/sub&gt;</th>
<th>&lt;i&gt;i&lt;/i&gt;&lt;sub&gt;Na&lt;/sub&gt;</th>
<th>&lt;i&gt;i&lt;/i&gt;&lt;sub&gt;Na&lt;/sub&gt;</th>
</tr>
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<td>∆E(AP&lt;sub&gt;10&lt;/sub&gt; + 20 ms)</td>
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<td>12.2</td>
<td>−4.2</td>
<td>−0.5</td>
<td>0.4</td>
<td>1.7</td>
<td>−0.6</td>
<td>−0.5</td>
<td>−2.4</td>
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<tr>
<td>∆E(AP&lt;sub&gt;30&lt;/sub&gt; + 20 ms)</td>
<td>8.8</td>
<td>5.4</td>
<td>−0.3</td>
<td>−0.4</td>
<td>0.8</td>
<td>6.4</td>
<td>−0.1</td>
<td>−0.1</td>
<td>−2.5</td>
</tr>
</tbody>
</table>
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Figure 1. Effect of transient releases of a virtual muscle on APD in various phases of AP. (a) the change in length (L), force (F), and membrane potential (E) during an isometric contraction at the control muscle length (thick lines) and after short-time 5% release at different instants 1–4 (thin lines). Arrows indicate the instants in 20 ms after release (T_{rel} + 20 ms) at which the increments of the membrane potential are calculated (see Subsection 3.1.1). (b) the change in [Ca^{2+}]_{in}, Na^{+}–Ca^{2+} exchange current, i_{NCX}, slowly activated outward calcium current, i_{K1}, in the control (thick lines) and in response to deformations 1 and 3 (thin lines).

depolarizing component of the current i_{NCX} in the forward-mode phase (Fig. 1b).

In order to find out why the similar muscle shortening in different phases of AP plateau finally leads to a different increase in the APD, we used the method of integrals of difference currents (see Section 2). Table 1 gives the change in the membrane potential $\Delta E$ in 20 ms after release ($T_{rel} + 20 ms$), when the instant of the $T_{rel}$ release coincides with either AP10 or AP30 (in Fig. 1 these instants $T_{rel} + 20 ms$ are indicated by arrows). In the case of the earlier shortening, $\Delta E(\text{AP10} + 20 \text{ ms})$ is 5 mV and $\Delta E(\text{AP30} + 20 \text{ ms})$ is 8.8 mV. In Table 1, the values of the change in the membrane potential $\Delta E_{k}(T_{rel} + 20 \text{ ms})$, which are due to the change in a charge transferred by each individual ionic current $i_{k}$, are also compared.

As was expected, the method of integrals of difference currents showed that the main reason for additional depolarization $\Delta E > 0$ caused by the muscle release is the change in the potential $\Delta E_{NCX} > 0$, which is connected with the depolarizing difference current $\Delta i_{NCX} < 0$ between the test and control currents $i_{NCX}$ [recall that because of formula (2.3) $\Delta E_{k}$ and $\Delta i_{k}$ have opposite signs]. Note that in both cases $\Delta i_{NCX} < 0$ after release due to a decrease in the repolarizing component of the current $i_{NCX}$ > 0 in the reverse-mode phase (Fig. 1b).

A decrease in the slowly activated outward $K^{+}$ current, $i_{K1}$, also contributes to the depolarizing deformation effect (Fig. 1b). Indeed, the increment in the potential caused by the difference current $\Delta i_{K1} < 0$ is $\Delta E_{K1}(T_{rel} + 20 \text{ ms})$ (see Table 1). Note that a depolarizing increment in the potential $\Delta E_{NCX}(T_{rel} + 20 \text{ ms})$ under earlier de-
formations is larger than the corresponding increment $\Delta E_{K1}(T_{rel} + 20 \text{ ms})$, whereas under later deformations the reverse was true. Since the muscle release is produced at different values of the membrane potential, the current $i_{K1}$ was activated differently by the moment of deformation and $\Delta E$ variously affects the change in this current. Under the earlier deformation when the value of the membrane potential is rather large, the absolute value of the current $i_{K1}$ is smaller and its sensitivity to the change in the potential, which is assessed by the value $d_{K1}/dE$, is also smaller than that for the muscle shortening at the lower level of the potential. Therefore under delayed muscle shortenings in the plateau phase (but the potential level is still larger than $-65 \text{ mV}$) there is a relatively large decrease in $i_{K1}$ and, as a consequence, a longer delay in the completion of the repolarization phase than that in the case of muscle shortening in the initial phase of plateau (Fig. 1b).

With the instantaneous muscle release after the completion of repolarization the difference currents $\Delta i_{NCX}$ and $\Delta i_{K1}$ are differently directed. At the values of the membrane potential close to those of the resting potential an additional amount of $[\text{Ca}^{2+}]_{\text{in}}$ caused by shortening increases the value of the depolarizing component $i_{NCX} < 0$, whereas a small increase in the potential (to the level no larger than $-65 \text{ mV}$) leads to an increase in repolarizing $i_{K1} > 0$. Thus, the total change in the AP results from a subtle balance between the changes in these two currents and, as a rule, total $\Delta E$ is not large.

The changes in the depolarizing $\text{Ca}^{2+}$ current via L-channels, $\Delta i_{\text{calL}}$, also affect the change in AP. In the case of muscle shortening at the AP10 level, an increase in $[\text{Ca}^{2+}]_{\text{in}}$ leads to the acceleration of the inactivation of $i_{\text{calL}}$, which decreases its

![Figure 2](image)

**Figure 2.** Effect of the short-time stretch of a virtual muscle on AP. Protocols of the change in length are shown on the top panels. APs during the control isometric contraction (thick lines) and after stretch-release deformations (QS-QR, thin lines) are shown below. The results are obtained for different parameters of conductivity of mechanosensitive channels $g_{\text{MSC}} = 0.013$ (middle row of plots) and $g_{\text{MSC}} = 0.09$ (bottom row of plots).
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Figure 3. Extra APs caused by deformations. The virtual muscle was instantly released (a) or stretched (b) shortly before the completion of the next AP during the control isometric contraction (thick lines). (a) the change in muscle length ($L$), $[Ca^{2+}]_{in}$, $Na^+-Ca^{2+}$ exchange current ($i_{NCX}$), and membrane potential ($E$) in response to the instantaneous 11% shortening (thin lines). (b) the change in muscle length, the current via mechanosensitive channels $i_{MSC}$ and membrane potential ($E$) in response to 5% stretch (thin lines).

depolarizing influence on the membrane potential, i.e. $\Delta E_{CaL} > 0$, which inhibits an increase in the potential. Under delayed deformation, $\Delta E_{CaL}$ does not greatly affect the total change in the AP.

We also investigated the dependence of the APD on the deformation duration, the shortening amplitude, and the shortening velocity. Under the above mechanical perturbations, the APD increased as compared to the control value as the value of perturbations increased. The results of the numerical experiments are also in good agreement with the earlier published experimental data [8].

3.2. Effect of a transient stretch on the action potential

In the framework of the model that takes into account the currents via the mechanosensitive channels $i_{MSC}$ at the two values of conductance of the mechanosensitive channels $g_{MSC}$: low ($g_{MSC} = 0.013 \mu S$, Fig. 2, middle row of plots) and high ($g_{MSC} = 0.09 \mu S$, Fig. 2, bottom row of plots), we investigated the effect of a short-time stretch on the heart muscle activity. The virtual muscle was instantly stretched by 5% of the control length (the initial sarcomere length in the control cycle was 2.1 $\mu m$), then kept at this level for 30 ms, and afterwards returned to the initial level.

Under cyclic deformations, in the early phase of plateau of the control AP (at the
level over 25% of repolarization for $g_{\text{MSC}} = 0.013 \mu\text{S}$ or over 20% of repolarization for $g_{\text{MSC}} = 0.09 \mu\text{S}$) the membrane potential abruptly decreased in response to a muscle stretch and then returned to the control AP after the restoration of the control muscle length and, as a result, even became longer (Fig. 2a).

As the moment of a stretch shifted to lower potentials but higher than the reverse potential for $g_{\text{MSC}}$ ($E_{\text{MSC}} = -20 \text{ mV}$, [29]), the repolarization acceleration after a stretch led to the APD reduction as compared to the control one (Fig. 2b). Further, at the stretch level somewhat larger than the reverse potential for $g_{\text{MSC}}$ there occurred a crossover of the time course of repolarization as compared to the control one (Fig. 2c). This crossover was pronounced only at sufficiently large values of conductance $g_{\text{MSC}}$. Only in this case, the initial acceleration of repolarization right after a stretch could be overlapped by the depolarizing current that occurred upon reaching the reverse potential for $g_{\text{MSC}}$.

Finally, at larger $g_{\text{MSC}}$ a further shift of the beginning of a stretch below the reverse potential for the mechanosensitive channels led to a lengthening of the AP (for example, in stretching at the AP$_0$ level, Fig. 2d, bottom row of plots), which was caused by the activation of the depolarizing current via the mechanosensitive channels.

The above results of modelling are in good agreement with the experimen-
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Figure 5. Change in $\text{Ca}^{2+}$ input-output via the cell membrane in transition from the isometric to isotonic regime of contractions. The total $\text{Ca}^{2+}$ influx in a cell during the cycle consists of the $\text{Ca}^{2+}$ influx with calcium current via L-type channels ($i_{\text{CaL}}$, black bars) and with reverse mode $\text{Na}^+–\text{Ca}^{2+}$ exchange current ($i_{\text{NCX}}$, grey bars). On transition to the isotonic regime the amount of $\text{Ca}^{2+}$ entering a cell decreases (cumulative black + grey bars) mainly due to a decrease in the influx with $i_{\text{NCX}}$. The extrusion of $\text{Ca}^{2+}$ from a cell is provided by the forward mode $i_{\text{NCX}}$. The total amount extruded from a cell in one cycle (white bars) also decreases in transition to the isotonic regime and to a greater extent as compared to the input. The temporal input-output unbalance provides $\text{Ca}^{2+}$ accumulation in SR ($\text{SR Ca}^{2+}$ gain) (see the inset).

3.3. Extra action potentials mechanically induced by a release or stretch

In this paper, in the framework of our model, we reproduced and explained the experimental data of the occurrence of delayed afterdepolarization and an extra action potential in the heart preparation as a result of either its shortening [8] or stretch [11, 29] shortly before or after the completion of a successive AP (Fig. 3).

3.3.1. Extra action potentials induced by a release. As shown in Subsection 3.1, the 5% muscle shortening due to an instant release near the AP completion did not lead to overcoming the threshold depolarization level necessary for the occurrence of a new AP. However, when increasing the amplitude of virtual muscle release (for example, beginning with 11% shortening in the example in Fig. 3a) there occurred an extra AP caused by an increase in the depolarizing component of calcium-dependent $i_{\text{NCX}}$ in response to a splash of $[\text{Ca}^{2+}]$, due to the deformation. The extra AP caused by shortening is 35% shorter than the regular AP. It essen-
tially has no early repolarization phase and the plateau phase is also shorter so that repolarization ceases faster than that in the regular AP.

Note that it was possible to initiate an extra AP in response to an abrupt muscle release and muscle shortening only in a very short time interval near the control AP completion (for 34 ms for a given virtual muscle). Thus, 11% muscle shortening by 238 ms of the cycle (Fig. 3a) was accompanied by the generation of a new AP. The same muscle shortening only by 1ms previously brought about additional depolarization but did not lead to the generation of a new AP. In the framework of the model (as shown in the Subsection 3.1) the physiologically justified ‘stability’ of AP with respect to mechanical perturbations in the delayed repolarization phase is due to an oppositely directed influence of the mechanically induced alterations of the currents $i_{\text{NCX}}$ and $i_{\text{K1}}$, which compensate each other in most cases, on the membrane potential.

3.3.2. Extra action potentials induced by a stretch. If we assume that the only transducer of a mechanical signal to an electrical one under deformation is intracellular Ca$^{2+}$, the muscle stretch would not have to lead to the occurrence of extra potentials because the intracellular Ca$^{2+}$ concentration must only be reduced due to an increase in the affinity of TnC for Ca$^{2+}$ when the muscle length increases. Therefore we failed to obtain an extra AP in response to a stretch in the framework of the model that does not take into account the kinetics of the mechanosensitive channels. Introducing in the description of the model the mechanosensitive channels with nonzero conductance, we could obtain extra APs in response to a stretch of the muscle.

In Fig. 3b the virtual muscle that contracts isometrically at control length (sarcomere length is 1.9 $\mu$m) was instantly stretched by 5% right after the control AP completion. In response to an increase in length we imitated the activation of the mechanosensitive channels prescribing the nonzero conductance $g_{\text{MSC}} = 0.13$ $\mu$S in the model. The occurrence of the depolarizing current $i_{\text{MSC}}$ was accompanied by depolarization up to a threshold value and, as a result, by the generation of an extra AP that had a smaller amplitude and duration than the regular AP. Note that at smaller values of $g_{\text{MSC}}$, 5% stretch did not lead to the additional AP occurrence.

4. SLOW TRANSITIONS IN THE ELECTROMECHANICAL ACTIVITY OF HEART MUSCLE

In the previous section, we presented the results of modelling the ‘fast’ electromechanical muscle responses right after the mechanical perturbations. Besides, we reproduced and analysed a number of ‘slow’ responses observed in physiological experiments, viz. transitions from one to another stationary state in stepwise switching from isometric to isotonic regimes of contraction and vice versa [13].

In the control cycle, the virtual muscle periodically contracted in the isometric regime at stimulation frequency 0.2 Hz. The initial muscle length corresponded to the initial sarcomere length 2 $\mu$m. On completion of a successive isometric cy-
cle the load on the muscle instantly became smaller amounting to 20% of the peak isometric force. Further, this load was kept constant so that the muscle began to contract cyclically in the isotonic regime. In view of the stepwise change in the load, the transition to the new stationary regime of periodic oscillations of the muscle length in the process of contractions was observed (Fig. 4). The muscle shortening amplitude gradually increased from cycle to cycle together with an increase in the duration of the contraction-relaxation cycle (Fig. 4a). Concurrent with the change in the mechanical muscle activity, there was a slow increase in the APD (Fig. 4c). During the first cycle, upon transition to the new regime the APD contractions increased by 20 ms (5%). On reaching the steady state an increase in the APD at the level of 90% repolarization was 27 ms (7%) as compared to the APD in the control isometric contraction. The above results of the numerical experiments are in good agreement with the experimental data (see Fig. 2 in [13]).

Unlike the physiological experiment in which only the transitions of the change in mechanical activity and the AP were recorded, in the numerical experiment we could observe intracellular processes responsible for the slow mechano-electric effects. Thus, a gradual increase in the contractile muscle activity upon transition to the isotonic regime occurs on the background of an increase in the amplitude of Ca$^{2+}$/B7 transients from cycle to cycle, which on reaching a new stationary level exceeds by 20% the amplitude of the Ca$^{2+}$ transient in the isometric cycle (Fig. 4b). The duration of Ca$^{2+}$ transients also gradually increases.

A slow change in the time course of the Ca$^{2+}$ transient, upon switching to isotonic contractions, is caused directly by both the change in the mechanical conditions and a gradual change in the Ca$^{2+}$ contents in a cell (Fig. 4d). The transition to isotonic contractions, i.e. dynamic changes in the muscle length during each contraction entails a decrease in the affinity of TnC for Ca$^{2+}$ as compared to the isometric conditions, which leads to a faster decay of Ca–TnC complexes in the cycle and, as a consequence, to some increase in [Ca$^{2+}$]$_{in}$ in the initial phase of decline in the Ca$^{2+}$ transient. The change in the [Ca$^{2+}$]$_{in}$ kinetics in turn substantially affects the calcium fluxes in and out of a cell as well as Ca$^{2+}$ absorption in SR. In particular, the amount of calcium that enters a cell from the outside slightly decreases (Fig. 5) mainly due to a decrease in a Ca$^{2+}$ influx with reverse-mode $i_{NCX}$. Note that in view of the redistribution of the calcium fluxes there occurs a crossover of Ca$^{2+}$ transients in the delayed phase of decline, i.e. by the end of Ca$^{2+}$ transients the level of [Ca$^{2+}$]$_{in}$ in the isotonic cycle is below this level in the isometric cycle (Fig. 4b). In view of the above dynamic changes in [Ca$^{2+}$]$_{in}$ in the isotonic cycle, the total amount of Ca$^{2+}$ extruded from a cell with forward-mode $i_{NCX}$ decreases and it decreases to a greater extent than its input does (Fig. 5). As a result, the total input-output balance turns out to be in favour of a decrease in the output and hence the accumulation of some amount of Ca$^{2+}$ in a cell (Fig. 5). Thus, in view of the fine calcium regulation of $i_{NCX}$, there is a gradual accumulation of calcium in SR from cycle to cycle until the new stationary balance of Ca$^{2+}$ input-output in a cell from the intracellular space is set up, which corresponds to a higher level of calcium in SR and an increase in the contractile muscle activity (Fig. 5).
and the calcium kinetics in a cardiomyocyte change during transition, but the AP duration also changes. As in most of the above examples, the main trigger for AP modulation is mechanically induced changes in \( i_{\text{NCX}} \), especially in the reverse-mode phase. Seemingly, an increase in the AP duration was to provide a larger calcium influx from the outside of a cell with current \( i_{\text{CaL}} \). However, in our model, this small increase is essentially leveled by the calcium current inactivation in view of an increase in release from SR. In fact, it is not improbable that the contribution of the voltage-dependent modulation of this current to the calcium accumulation in transition is more substantial.

5. DISCUSSION

We developed the mathematical model of electrical and mechanical phenomena in the heart muscle [25]. Using this model in the present paper and in our previous studies [25, 26], we essentially reproduced all the experimental results available in the literature, which demonstrate the effect of the mechanical conditions of the contraction of cardiomyocytes on their electric activity. In the framework of the model we could establish the possible chain of events providing a link between the mechanical and electrical activities. The mechano-dependent modulation of the Ca–TnC complex kinetics and the calcium-dependent changes in \( i_{\text{NCX}} \), which are in most cases a trigger for the AP modulation, play an important role in this chain. The voltage-dependent alterations of other currents, in particular, quickly and slowly activated K\(^{+}\) currents and the persistent Na\(^{+}\) current, which regeneratively affect the progressive AP, can also substantially modulate the total deviation in the membrane potential from the control AP in response to a mechanical perturbation. Besides, currents via the mechanosensitive channels directly reacting to the muscle deformation can also substantially modulate the electrophysiological response to a mechanical perturbation.

Analysis of the model showed that at muscle shortening the mechano-electric feedback is mainly realized by the modulation of the Ca\(^{2+}\) kinetics (Figs. 1 and 3). Conversely, when the myocardium is stretched, the contribution of the mechanosensitive channels to the change in the potential can prove dominant and can be either added to the influence of the alteration of the calcium-dependent currents or oppositely directed (Figs. 2 and 3). Analysis of the model allows us to explain the apparent contradictions in the experimental data demonstrating the opposite AP responses to the stretch of heart preparations [1, 11, 28]. The model predicts that the response of cardiomyocytes to stretch can really be quite diverse: the AP can be either shortened or lengthened and the crossover of the repolarization with respect to the control AP can be observed (Fig. 2). The character of the changes in the AP will depend both on the experimental conditions and the individual electromechanical properties of cardiomyocytes.

In the framework of the model, we found the conditions under which both the abrupt shortening and stretch of the heart preparation can cause extra APs (Fig. 3). To this end, the perturbing deformations must be no less than some threshold am-
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plitude and must also fall into a certain rather short time interval of the progressive AP. Thus, our results allow us to suggest that there exists in norm an extremely small range of vulnerability of the electrical activity of cardiomyocytes when an abrupt mechanical perturbation (shortening or stretch) can lead to an extra excitation of myocardium and provoke the rhythm disturbance. For example, the cases of commotio cordis are known in the clinical practice: a sudden death from an impact in the chest as a result of fibrillation caused by an abrupt deformation of the cardiac muscle without its mechanical damage [19]. It was shown experimentally that the impacts responsible for arrhythmia occurred at a high rate and coincided with a certain phase of the membrane potential repolarization. Another example of the pathological effect of mechanical factors on the electric function of the heart is the occurrence of arrhythmias on the background of a collapse, i.e. a steep decline of vascular resistance and, as a consequence, a decrease in load on the cardiac muscle [10]. Note that unlike the stretch effects widely investigated in experiment and in clinic, the possible arrhythmic consequences of the abrupt unloading of the heart have not essentially been studied. The model predictions allow us to advance the hypothesis that with pathology the range of vulnerability of electric activity to myocardium deformation can increase as compared to the norm.

Slow responses (changes in the state during several cycles) analogous to the ones observed in isolated myocardium preparations [13] in switching from heavy loaded isometric contractions to low loaded isotonic contractions and vice versa were recorded in the intact heart under the abrupt change in vascular resistance. This transition of the change in the inotropic state depending on the load in the intact heart was called the Anrep phenomenon [24]. The mechanisms and the physiological significance of the Anrep phenomenon have not been understood so far. The model allows one at least partially to close this gap.

In the experiment on an isolated cardiac muscle in transition from the isometric to isotonic regime the muscle begins to shorten cyclically, which simulates the phase of cardiac output in the intact heart. During several cycles the amplitude of the shortened muscle increases (Fig. 4), which matches an increase in an ejection fraction. An increase in cardiac output in the intact heart is associated with a larger volume of venous return and hence an increase in the amount of blood flowing into a ventricle in diastole. In order for the influx of an increasing blood volume to be effective, the ventricle must relax faster as the cardiac output increases. The experiments on the model show that in transition to isotonic contractions, together with a decrease in finite systolic muscle length, we observe a significant increase in the rate of the isometric relaxation phase (on the ejection completion), which is in agreement with the physiological predictions. Thus, the maximum rate of the isometric relaxation phase increases by 60% in the first isotonic cycle and by the end of transition it is twice larger than the maximum rate of relaxation in the isometric cycle. According to the model predictions, the changes in the inotropic state of the muscle and the relaxation characteristics, which, in the framework of intact heart, would allow one to increase the ejection fraction without increasing the finite diastolic volume, are closely connected with the change in the AP duration and the change in the calcium- and voltage-dependent Ca$^{2+}$ fluxes in cardiomyocyte, which provide an increase in
the Ca$^{2+}$ level in SR.

In conclusion, we emphasize that the immune or autoimmune processes in myocardium, for example, with myocarditis can substantially affect the viscoelastic properties of myocardium, ionic channels, ionic pumps, and ion exchangers in cardiomyocytes, as we showed earlier on myocardium preparations in patients suffering from a rheumatic heart disease [20]. We believe that our model is adequate for the analysis of pathophysiological mechanisms of this kind of disturbances of the electromechanical function of myocardium.

REFERENCES


