Excitation model of pacemaker cardiomyocytes of cardiac conduction system

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Abstract. Myocardium includes typical and atypical cardiomyocytes – pacemakers, which form the cardiac conduction system. Excitation from the atrioventricular node in normal conditions is possible only in one direction. Retrograde direction of pulses is impossible. The most important prerequisite for the work of cardiomyocytes is the anatomical integrity of the conduction system. Changes in contractile force of the cardiomyocytes, which appear periodically, are due to two mechanisms of self-regulation – heterometric and homeometric. Graphic course of the excitation pulse propagation along the heart muscle more accurately reveals the understanding of the arrhythmia mechanism. These models have the ability to visualize the essence of excitation dynamics. However, they do not have the proper forecasting function for result estimation. Integrative mathematical model enables further investigation of general laws of the myocardium active behavior, allows for determination of the violation mechanism of electrical and contractile function of cardiomyocytes. Currently, there is no full understanding of the topography of pacemakers and ionic mechanisms. There is a need for the development of direction of mathematical modeling and comparative studies of the electrophysiological arrangement of cells of atrioventricular connection and ventricular conduction system.

1. Introduction
The most important features of the myocardium are automatism, excitability, conductivity, contractility and refractivity. Automatism of the heart lies in the ability of rhythmic contractions of myocytes under the influence of the pulses, occurring in the heart.

The myocardium includes typical and atypical cardiomyocytes – pacemakers, which form the cardiac conduction system. The latter provides automatism of cardiac contractions, as well as the coordination of the contractile function of myocardium of atria and ventricles. The first sinoatrial node of the system is a major center of automatism, i.e., the first-order pacemaker. Excitation is transmitted from the sinoatrial node to the cells. It reaches the atrioventricular node (second-order node) going along special conducting bundles from the atria. Atrioventricular node can generate pulses itself. Excitation from the atrioventricular node in normal conditions is possible only in one direction. Retrograde direction of pulses is impossible. Third-order node provides rhythmic automatism of the heart action. It is located in the bundle of His and in the Purkinje fibers. Automatism centers, which are located in the conduction system of the ventricles, are called third-order pacemakers. The frequency of myocardium activity is generally defined by sinoatrial node. It governs all underlying conductive system formations, and it “pushes” its rhythm upon them [1, 2].
Excitability of myocardium occurs under the influence of various stimuli: chemical, electrical, thermal and others that determine the ability to go into a state of excitement. The basis for this phenomenon is the negative electric potential which occurs in the initially excited area. Membrane of working cardiomyocytes in the excited tissue is polarized. It has a positive charge outside, and negative charge inside. This condition is caused by different concentrations of Na+ and K+ at both sides of the membrane. Different permeability of the cell membrane for these ions plays certain role. No Na+ ions penetrate the heart cells membrane at rest. Potassium ions penetrate only partially. The diffusion of K+ ions emerging from the cell increases the positive charge on the surface. The inner side then becomes negatively charged. The cell receives sodium ions under the influence of any stimulus. At this time, negative charge occurs on the cardiomyocyte membrane surface and potential reversal is provided. The amplitude of the action potential of cardiomyocytes is about 100 mV or more. This potential in turn depolarizes membranes of adjacent cells. As a result, they develop their own action potentials, that is, the spread of excitation along other cells of the myocardium takes place.

The conductivity of the myocardium is connected with the fact that the excitation waves go along its fibers at different speeds. Excitation along the atria propagates at a speed of about 0.8-1.0 m/s, along the ventricles at a speed of 0.8-0.9 m/s. At the same time it propagates along the special heart tissue at a speed of 2.0-4.2 m/s. Contractility of cardiomyocytes is due to the peculiarities of their structure. First atrial myocytes and then the papillary muscles with subendocardial layer of the ventricles are contracted. Then, the contraction process covers the inner layer of ventricles and thereby provides blood flow from the ventricular cavity to the aorta and pulmonary trunk. All changes to the contractile force of the cardiomyocytes, which appear periodically, are due to two mechanisms of self-regulation – heterometric and homeometric.

Refractoriness of cardiomyocytes is characterized by a decrease in tissue excitability throughout its activity. There are absolute and relative refractory periods. In case of electrical stimulation in the absolute refractory period the heart does not respond to the impact by stimulus and contraction. In addition, refractoriness continues as long as systole. In case of relative refractory period excitability of cardiomyocytes gradually returns to its initial level. However, in this case response of cardiomyocytes to the contraction can be above the threshold value. The relative refractory period is observed in atrial and ventricular diastole. The phase of the relative refractory is followed by the period of hyperexcitability. Moreover, it coincides with diastolic relaxation. It is characterized by the response of cardiomyocytes expressed by excitation flash even to the very small force pulses [3].

2. Review

To date, there is number of software and hardware systems, allowing observation of the reconstruction of the anatomical structure of the atria and visualization of the excitation dynamics: 1) CARTO - BiosenseWebster (USA); 2) EnSite- Endocardial Solutions (USA); 3) Bhotok-3D - research and production association (Tomsk); 4) Elkart-II navigator – Medical Industrial Company Electropulse (Tomsk).

These models have the ability to visualize the essence of excitation dynamics. However, they do not have the proper forecasting function for result estimation. Modern researches of excitation dynamics modeling, are aimed at scientific study of the heart as an object of study, or at modeling of the active medium property with its separate characteristic effects. In clinical practice, these techniques are not widely used due to their complexity also due to the high cost of individual model creation. Moreover, it is impossible to use reference solutions due to their uniqueness [4].

From the perspective of mechanics heart muscle is a complex multi-level system. Its behavior is predetermined by the two components. Passive, which is connected with the elastic and viscous properties of cardiomyocytes, defined as a composite material. Also active, which allows cardiomyocytes to perform their function of vascular blood flow provision. In this case mechanical activity of muscle takes place at the myocytes level and comprises contraction process. The contraction regulation consists of activation of actin filaments. It is caused and defined by changes in the content of cytosolic calcium. In turn, it is regulated by electric activation of the cell. At the same
time an action potential develops, which depolarizes the cell membrane. The action potential arising in
the myocardium to an external electrical pulse is conditioned by the participation of a number of
transmembrane ion currents, including sodium, calcium and potassium currents. This whole cascade of
processes is very complex and very significantly complicated by the presence of a number of
feedbacks. Mechanical conditions of contraction, as well as the process of cross-bridges cycling can
have significant impact on calcium and electrical activation of cells [5].

Thus, cardiomyocytes are very complex contractile “machine”. The principles of its arrangement
and behavior can be predicted only with the help of complex mathematical modeling. Currently, there
are certain developments and different mathematical models which describe myocardium/cardiomyocytes subsystems with varying level of detail. The models of passive
mechanical properties of cardiomyocytes, models of their active mechanical behavior, as well as the
model of the electrical activity of myocytes are described. However, there is still a significant lack of
integrative models that describe the existing subsystems taking into account feed-forward and
feedback between them. Integrative mathematical model allows for not only deep exploration of the
general laws of the myocardium active behavior, but also for determination of the mechanism of
violation of electric and contractile function of cardiomyocytes which accompany various cardiac
pathologies, as well as for development and introduction of new methods for correction of various
disorders. The possibilities of integrative methods for clinical practice are demonstrated by the
analysis of the mechanism and methods of correction of arrhythmias that occur in case of calcium
overload of cardiomyocytes, which take places in many diseases of the heart. This model helps to
predict the role of mechanical and electrical feedback in the pathogenesis of the heart rhythm
disturbance [6].

Developed comprehensive integrative model of cardiomyocytes provides the possibility of building
one-, two- and three-dimensional models of the myocardium, in which electrical excitation and
mechanical interaction between segments are matched with the development of action and stress
potentials in the cells, considering feed-forward and feedback on the intracellular and tissue levels [7].

Modern muscle biomechanics accumulated contraction conditions that modulate the contractile
activity of cardiomyocytes. Shifts and slopes of normalized isometric curves plotted at the contraction
at different concentrations of constant calcium activation were changed in direct dependence on the
degree of initial stretching of the studied cardiomyocyte preparation. The results are obtained
repeatedly by many authors in the cardiomyocytes of different animals. It is noted that for the
cardiomyocyte (unlike skeletal) contraction at constant activation is an artificial experimental mode,
which requires its skinning (demembranization). More natural preparation is experiments with a
response to an electrical pulse. There is a process of calcium transition in the cytosol of
 cardiomyocytes. This is rapid increase in the concentration of calcium, which is replaced by its
decline.

Experimental conditions revealed effects indicating that the initial mechanical conditions of
contraction subsequently affect its further course. The effect of short cyclic deformation occurs when
in the course of isometric cycle myocyte undergoes drastic change in length (shortening or elongation)
by a certain percentage, and then after a few milliseconds it is returned to the original length.
Thereafter, the process of isometric contraction development occurs at this length differently than in
cases where there is no deformation. In this case there is inactivation of contraction due to the fact that
after the deformation the force level becomes lower and contraction-relaxation cycle ends faster.
Inactivation occurs faster if it is deformed later during the cycle. This effect is especially pronounced
in the deformation in the relaxation phase. The most important effect demonstrating the influence of
mechanical impact on the development of contraction/relaxation cycle is the load depending
relaxation. The essence of this phenomenon consists in the fact that the isotonic cycle ends much
faster than isometric one. There is direct dependence on the load: the lower the load, the greater the
difference between the duration of isometric and isotonic cycle. This is due to the paradoxical
properties of isotonic cycles. The lower the load, the higher the speed of myocytes stretching under
this load in the stage of relaxation. There are other features depending on various modifications of mechanical conditions, in addition to these cyclic deformations and load dependence [8].

The explanation of such phenomena lies in the assumption about modulating effect of mechanical conditions on the processes of calcium activation of contractile proteins. They affect the affinity of troponin C to calcium as calcium and troponin complex (CaTpC) play a key role in the regulation of cardiomyocyte mechanical activity. The formation of CaTpC complexes is accompanied by conformation of tropomyosin filament within the functional group. The latter consists of a fragment of the actin filaments (7 monomers), tropomyosin filaments which cover the center of the myosin head attachment to actin, as well as of troponin, which is located on tropomyosin.

The tropomyosin conformation reveals binding sites on the actin filament. This creates the necessary conditions for the formation of cross-bridge. The cross-bridge undergoes several specific stages of existence that are associated with the utilization of the ATP energy. The most important from the point of view of mechanical function are: force generating turn, which is a source of active stress and movement of actin towards myosin filaments (i.e. shortening); disconnecting of myosin head from actin, i.e. bridge detachment.

There are feedbacks between the mechanical conditions and calcium activation in cardiomyocytes. Mechanical and electrical feedbacks are explained by the fact that they are a consequence of ion currents through mechanic-sensitive channels. Studies which included recording of free intracellular calcium and the action potential (AP) during contraction, revealed the dependence of changes of all parameters of AP duration as a result of mechanical conditions (active shortening, deformation, load change) which occur simultaneously with changes in the shape and duration of calcium transition. This consistency conceptualizes the influence of mechanical conditions on the excitation of the cells. Their electrical activity takes place indirectly through a mechanical modulation of the intracellular calcium kinetics. It is very difficult to define the role of different mechanisms responsible for mechanical-calcium and mechanical-electrical feedback in complex and multi-level systems such as myocardium. This is revealed by using mathematical modeling [9, 10].

Models of ionic currents responsible for the formation of AP in cardiomyocytes were actively developed by many researchers. Together with Denis Noble models there are such known models as Luo&Rudy and its various modifications, model of Winslow group, a number of continuum models of macro-level processes with respect to the mechanical interaction or conduction of electric excitation in segments of the cardiac tissue, models of electromechanical coupling in multicellular segment. Despite the presence of a large number of models, description of the activation of cardiomyocytes is extremely simplified in all macroscopic models. The intracellular mechanisms that are responsible for feedback of electrical and mechanical activity are not considered at all.

The term “mechanical heterogeneity” means differences of mechanical characteristics of various interacting myocardial segments. These may be individual cardiomyocytes, sarcomeres or large sectors of the heart chamber walls. To some extent, the arranged heterogeneity is the property of normal myocardium. Most cardiac pathologies are accompanied by destruction of heterogeneous structure with increasing dispersion of mechanical properties of the ventricle wall. Mechanical heterogeneity is present at the molecular level. It is manifested in the change of ratios of the various isoforms of myosin (V1 and V3) in cardiomyocytes depending on their location. Under normal conditions, the ratio V1/V3 gradually increases in a direction from endocardial to epicardial layer.

Conditions of mechanical contraction of cells in a heterogeneous myocardial system directly depend on the mechanical properties of other cardiomyocytes interacting with it. Circuit of mechanical-calcium and mechanical-electrical feedbacks affect the course of the cell development (stress and/or shortening). This, in turn, affects the mechanical condition for contraction of neighbor cells. The resulting feedback circuit causes changes in mechanical behavior. Then mechanical conditions (stress and deformation fields) created by the interaction of cardiomyocytes are changed again. Mechanical conditions of contraction of each element of the system depending on dynamic changes in the properties of the other elements are modified dynamically in the process of continuous interaction. Process of continuous adjustment of the system elements to each other complicates the
prediction of the behavior of each component and the system as a whole. As a consequence, the study of the phenomenon of mechanical heterogeneity requires more simplified experimental and theoretical models that provide the opportunity to identify and analyze the essential properties of the mechanical interaction of the elements of a heterogeneous system.

Methods of muscle duplets represent a pair muscle fibers or cardiomyocytes connected in series or in parallel and having mechanical interaction with each other. There are 6 duplet configurations implemented: 1) serial and parallel natural duplet (2 living muscles connected either in series or in parallel); 2) serial and parallel virtual duplet (a pair of virtual muscles or cardiomyocytes connected in series or in parallel); 3) serial and parallel hybrid duplets (living muscle in real time interacts with a virtual partner (living muscle attached to the levers of installation, the virtual object is simulated by computer). In various variants of virtual and hybrid duplets virtual elements were represented by different versions of mathematical models using models of active mechanical behavior of the myocardium and using versions of models of electromechanical coupling Yekaterinburg-Oxford (E0-2003 and E0-2006). One of the kinds of muscle duplets is a virtual serial duplet, which is based on the model E0-2006. It is used for theoretical studies of the influence of mechanical conditions in the occurrence of arrhythmia in case of overload of cardiomyocyte with calcium ions.

According to the principle of minimal sufficiency, each following extension allows for simulation of other new phenomena, and further clarification of the role of the additional parameters included in the model of the process and implementation of phenomena.

Mathematical models of the mechanical activity of the myocardium fully reproduce all the basic relationship of cardiomyocytes contraction-relaxation cycle in isotonic, isometric and physiological mode. It helped to find a mechanism that provides effect of mechanical conditions of contraction on the course of the calcium activation of myocytes. The basis of this effect is the cooperative interaction of regulatory substances, contractile proteins, as well as the dependence of the probability of formation of bridges on the available length of the sarcomere. In case of severe myocardial hypertrophy reduction in load dependence to complete disappearance is conditioned by the slowdown in the calcium absorption in the sarcoplasmic reticulum (SR). This is due to increased blocking of calcium ATPase in SR. The effect of the calcium pump speed in SR on load dependence is ambiguous. The load dependence declines as a result of lowering of the pump function be means of strengthening of its blockade, and also be means of its rising due to the increase in the speed of Ca2+ transfer by calcium ATPase molecules in SR. Myocardium viscosity affects the mechanical activity of myocardium. The viscosity of the end areas of the modules of the myocardium causes mismatch between the temporary increase in isometric contraction and shortening of the sarcomeres. The viscosity of the deep areas of preparations significantly modulates relaxation. It has an impact on the speed of this process. Combination of model of mechanical activity and electrical activity of “Noble-98” provides a new circuit of mechanic-electrical feedback. It arises from the interaction of Na-Ca of exchange current in myocardium and also due to the cooperative action of cross-bridges on the reciprocity of troponin C to calcium ions. The model allows for prediction of the ability of the feedback to perform function of trigger for the occurrence of acute heart failure in the event of calcium overload of cardiomyocytes. Ways of correction of this pathology are possible within this model [11, 12].

3. Conclusion
Analysis of the contemporary literature has shown that lateral areas of atrioventricular connection are studied fragmentarily; majority of further investigations are carried out on its central area, atrioventricular node, and limited mainly to the questions of excitation propagation; its pacemaker properties are studied to lesser extent. Question of the pacemaker arrangement of atrioventricular connection seems to be urgent. Idea of automatic activity of cells in the atrioventricular cusps is formed only on the basis of work performed on the heart of mammals. Processes underlying the diastolic depolarization of the subsidiary pacemakers cells in the atria are much less studied. The problem of accurate localization of atrial pacemakers requires new experimental studies; there is a need for revision of their data on topography. Obviously, these data are important not only
theoretically but also clinically as pacemaker cells, in particular those in atrioventricular cusps represent a potential source of formation of ectopic pulses that can cause arrhythmia of supraventricular origin. Comparative aspects of this problem are still not sufficiently developed. The sufficient analysis of the formation of the atrioventricular connection in the course of vertebrate phylogeny was not conducted too. Pacemaker properties of cells of the atrioventricular heart area of fish, reptiles and birds are almost unexplored. There is no information about the ontogenetic changes of pacemaker function of atrioventricular connection [4, 13, 14].

Thus, currently there is no complete understanding of the topography of pacemakers and ionic mechanisms underlying functional properties of the cells constituting this very important area of the heart. There is a need for the development of direction of mathematical modeling and comparative studies of the electrophysiological arrangement of cells of atrioventricular connection and ventricular conduction system.

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