THE UNKNOWN MYOCARDIUM

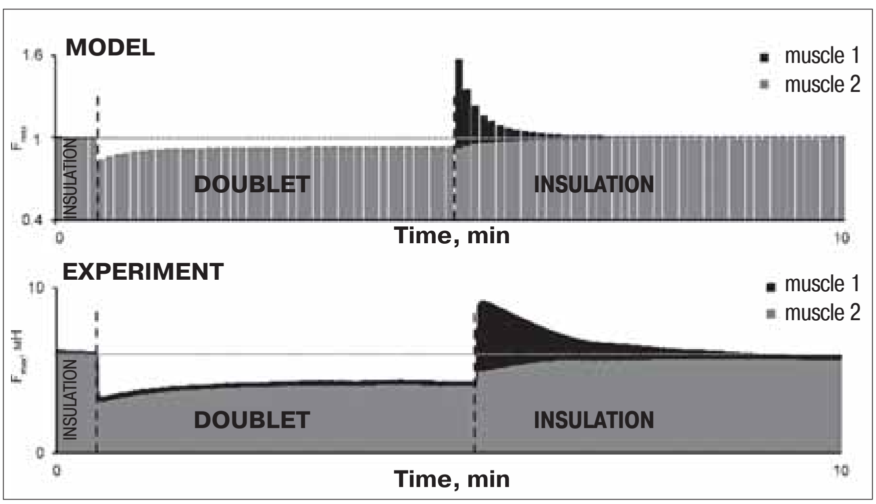
by Yelena PONIZOVKINA, journalist

A group of scientists from the Institute of Immunology and Physiology, the Ural Branch of the Russian Academy of Sciences (Yekaterinburg), headed by Vladimir Markhasin, Corresponding Member of the Russian Academy of Sciences, a specialist in the cardiac biomechanics, well-known both in Russia and abroad, has discovered a new type of myocardial contractility autoregulation connected with myocardial tissue heterogeneity. This result is important for a diagnosis, therapy, and prognosis of cardiovascular diseases, which rank first among the causes of population mortality. The innovational work of physiologists has become one of the most important achievements of the Ural Branch of the Russian Academy of Sciences of recent years.

Not long ago scientists believed that myocardial cells—cardiomyocytes—were relatively similar. When numerous data indicated the opposite, the scientists started to speak about myocardial heterogeneity. It was found that the biomechanical, bioelectric, and biochemical characteristics of cardiomyocytes in different regions of the ventricular wall (at the apex or base, in the outer or inner layers) were different, and with propagation of stimulation wave in the heart were stimulated not simultaneously, but in succession. This phenomenon was first discovered in the course of studies of pathological processes, for example, coronary disease or myocardial infarction. Further experiments showed that the normal myocardium was also heterogeneous. Moreover, this property was responsible for the normal work of the main organ of the circulation system, preventing the development of arrhythmia. Due to this the myocardium acquires high plasticity: reduced function of one region of the compartment wall can compensate for stimulation of others.

The Ural cardiophysiologists got interested in these effects. In order to understand the role of this heterogeneity in health and disease, a group of specialists at the Institute of Physiology, the USSR Academy of Sciences Ural Scientific Center, created in the 1980s-early 1990s a mathematical model of mechanical activity of the myocardium. This group of scientists included Prof. Valery Izakov, RAS Corresponding Member Vladimir Markhasin, Leonid Katsnelson, Dr. Sc. (Phys. & Math.), and later—Olga Solovyova, now Dr. Sc. (Phys. & Math.). Recently this model was improved and developed in collaboration with colleagues from the Oxford University (UK): in addition to the mechanical and chemical, it now includes a description of electric phenomena, developed by Dennis Noble, an outstanding British physiologist, the founder of *Physiom* International Proj-

Ural cardiophysiologists, authors of discovery of a new type of myocardial autoregulation. Row 1, left to right: Yuri Protsenko, Vladimir Markhasin, and Olga Solovyova; row 2: Oleg Lukin, Alexander Balakin, and Pavel Konovalov.



Slow inotropic response in a doublet consisting of 2 electrically and mechanically asynchronous muscle elements. Changes in the muscle force peaks in the contractile cycle before, during, and after they are united in a doublet.

ect. Now this model is known in literature as the Yekaterinburg-Oxford (EO) model. The system of nonlinear common differential equations explains an extensive range of experimental data obtained on myocardial preparations under conditions of various contraction modes and exposure to mechanical factors, allows to predict effects, later experimentally confirmed on physiological models of heterogeneous myocardium—muscle doublets (two muscles connected in succession or simultaneously).

Let us note that the doublets can be biological (consisting of two live muscles), virtual (when the elements are represented by mathematical models), or hybrid (when the biological muscle works with a virtual partner—mathematical model). The virtual muscle gets excited, contracts, behaves under load as live. Using these models, the scientists have studied the mechanical and electric effects of myocardial heterogeneity at all stages: an isolated muscle working individually, together with others, and separated from them. It is essential that various regions of the cardiac compartment walls are stimulated in a certain sequence. The effect of this stimulation can be evaluated if each of the muscles in the doublet is stimulated with an artificial delay. According to Markhasin, time in this case acts as a creative factor.

How myocardial cells become heterogeneous? Let us assume that a chain of these cells has 10 segments, explains the scientist. In case of successive stimulation, previously activated segments will shorten and contract, stretching still inert segments, as mechanical interaction between them is rapid—with a velocity of mechanical wave propagation—300 m/sec. The velocity of electric wave in the working myocardium is much slower—0.3 m/sec, and as it reaches last segments, they turn out to be already stretched. Thus, electric stimulation of the first segments falls on their shortening, while of the last ones on stretching. This modifies significantly the pattern of myocardial electric activity, which, in its turn, affects the level and kinetics of calcium ions in the cells, determining the force of myocardial contraction. As a result, the homogeneous system becomes heterogeneous in response to successive stimulation of its elements. Changes in the function of this chain can be verified in experiments on doublets. These experiments have revealed a new type of the so-called slow inotropic (affecting the myocardial contractility) response—Slow Force Response (SFR).

Several types of SFR to external stimulation were known up to recent time. One of them consisted in gradual attaining of the maximum amplitude of cardiac contractions with heart rate increase; it was called the Bowditch scale (phenomenon) (after Henry Bowditch, an American physiologist, 1840-1911). Another one is explained by Frank-Starling's law, formulated by Otto Frank (1865-1944), a German physiologist, and Ernst Starling, an English scientist (1866-1927): in case of the myocardium distension, an immediate increase of the force of contraction is followed by a secondary multicycle increment by 30-40 percent. The third type was described in 1971 by Raymund Kaufmann, a German physiologist, and his colleagues. They found that the force of myocardial contraction slowly increased with transition from the isotonic mode (when the atrioventricular valves are closed, while the aortic one is open) to isometric (when all valves are closed). These slow myocardial responses are similar in one respect: they emerge as a result of external stimulation of the myocardium.

The Ural cardiophysiologists discovered a basically new SFR type, explained not by an external exposure, but by myocardial heterogeneity—the so-called intramyocardial slow inotropic response (SFRim), emerging as a result of mechanical interactions between the heterogeneous contractile elements of cardiac tissue.

At first this effect was revealed in model experiments at the Laboratory of Mathematical Physiology by Vladimir Markhasin, Olga Solovyova, Leonid Katsnelson, and Pavel Konovalov. Later on young scientists Alexander Balakin and Oleg Lukin, working under Yuri Protsenko, Dr. Sc. (Biol.), experimentally confirmed this effect by the doublet method. In both cases mechanical and electric slow responses of the myocardium and responses associated with intracellular calcium kinetics were detected. We should like to emphasize a key role of mathematical simulation in these results; it proved to be a unique source of new information—it gave an unexpected result, later confirmed by the physiological experiment. By the way, examples of this kind are rare in biology. Usually it is vice versa—experiments correct the numerical model.

Now the scientists faced an intricate problem—to trace the changes in the electrical activity in heterogeneous muscles throughout their doublet interactions. This was realized by the method of floating microelectrodes—tiny fragments of a micropipette, filled with saline. Its tip diameter is 0.5 μm. Such conductor is fixed on a fine silver wire 50 μm thick, which should remain in the cardiomyocyte during interactions between heterogeneous muscles. Alexander Balakin, Cand. Sc. (Biol.), made hundreds of microelectrode pricks and only in 3 cases recorded electric activity in the continuous mode in heterogeneous muscles at all stages: in an isolated state, united in a doublet, and in a separated state. As a result, we have a complete picture of its changes before, during, and after the exposure. The studies of Oleg Lukin, Cand. Sc. (Biol.), from the laboratory of biological mobility, also played an important role. He measured concentrations and kinetics of calcium ions in the cells of the doublet elements, with the muscles isolated, united, and separated. His work won the Prize for young scientists of the Sverdlovsk Region Governor in 2012.

The numerical experiments on models and physiological tests have demonstrated that interactions between the heterogeneous segments of the myocardium cause their deformation, this, in its turn, leads to depression of certain genes. New types of contractile proteins and proteins regulating electric phenomena emerge in the myocardium under these conditions. The pattern of myocardial contractility is thus changing, its work adapts to the conditions of the moment, indicating its high plasticity.

In conclusion just a few words about the practical significance of the basic result. Studies of the myocardial heterogeneity phenomenon are important at least because this effect augments in case of pathology and essentially reduces the pumping function of the main organ of the circulatory system. It is also noteworthy that changes in the sequence of myocardial cell activation can lead to profound disorders in the mechanical and electric functions of the heart. There are cases when they emerged as a result of the pacemaker implantation. The Ural specialists recommend to place the electrodes in operations of this kind in accordance with the physiological sequence of myocardial stimulation.

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