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Mechanisms of vibration-induced structural myocardial remodeling

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ABSTRACT

The review analyzes literature data on structural changes in the heart of patients with vibration disease, as detected by echocardiographic methods. Particularly, it highlights concentric remodeling of the left ventricle chambers and disturbances in diastolic function. The review also discusses a 1.2-fold decrease in heart structure intensity compared to healthy individuals ($p < 0.05$). Furthermore, it examines changes in morphometric and bioenergetic parameters of cardiomyocytes under different experimental vibration modes (7 and 56 sessions at a frequency of 8 Hz), confirming the disruptions in the relationship between the spatial configuration of the heart cavities, contractile ability, and energy supply potential. Loss of cardiac myofibrils represents the transition from myocardial hypertrophy to decompensation, accompanied by an increase in degenerative (dystrophic) signs such as the loss of sarcomeres in cardiomyocytes. Understanding these pathological (morphological) processes requires consideration of various mediators that regulate cell metabolism, proliferation, growth, and survival, including stromal interaction molecule, calcium ATPase of the endo(sarco)plasmic reticulum, inositol-1,4,5-triphosphate receptor, protein that forms CRAC channels, and transient receptor potential canonical. The degradation system of the extracellular matrix, including matrix metalloproteinases and tissue inhibitors, plays a crucial role in structural cardiac remodeling. This system regulates the rate of mRNA synthesis on the DNA matrix by binding to specific DNA regions that control cardiac nutrition and plasticity. The review suggests that these findings can help explain some patterns of cardiac remodeling development in patients with vibration disease and determine the direction of pathogenetically based therapy. This therapy should consider not only the vibration-protective effect of drugs but also their ability to inhibit and regress myocardial remodeling.

Keywords: vibration; myocardial remodeling; prohypertrophic transcription factors; biomarkers of collagen metabolism; metalloproteinases.

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Механизмы структурного ремоделирования миокарда на фоне воздействия вибрации

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АННОТАЦИЯ

В обзоре представлен анализ литературных источников, посвященных изучению структурных изменений со стороны сердца у пациентов с вибрационной болезнью, выявленных с помощью эхокардиографических методов исследования в виде концентрического ремоделирования камер левого желудочка и нарушения его диастолической функции, снижения интенсивности работы структур сердца по сравнению со здоровыми людьми в 1,2 раза ($p < 0,05$). Анализ морфометрических и биоэнергетических показателей кардиомиоцитов на фоне различных экспериментальных режимов вибрации (7 и 56 сеансов с частотой 8 Гц) подтверждает нарушение идеального соотношения между пространственной конфигурацией полостей сердца, способностью к сокращению и обеспеченностью энергетическим потенциалом. Утрата миофибрилл клетками сердца символизирует переход гипертрофии миокарда в стадию декомпенсации и нарастание дегенеративных (дистрофических) признаков, в частности утраты саркомеров кардиомиоцитов. Для реализации процессов патологической структурной (морфологической) и энергетической перестройки ткани под воздействием вибрационно-опосредованных гемодинамических и ишемических факторов необходимо вовлечение в процесс многочисленных посредников, регулирующих метаболизм, пролиферацию, рост и выживание клеток, таких как STIM (молекула стромального взаимодействия), SERCA (кальциевая аденозинтрифосфатаза эндо(сарко)плазматического ретикулума), IP3R (рецептор инозитол-1,4,5-трифосфата), Orai (белок, формирующий CRAC каналы), TRPC (канонические каналы транзиторного рецепторного потенциала) и др. В качестве одного из важнейших звеньев структурного ремоделирования сердца выступает система деградации экстрацеллюлярного матрикса, включающая матриксные металлопротеиназы и их тканевые ингибиторы, регулирующие скорость синтеза мРНК на матрице ДНК путем связывания со специфическими участками ДНК контроля сердечной трофики и пластичности. Большое количество проанализированных фактов позволяет объяснить некоторые закономерности развития ремоделирования сердца у пациентов с вибрационной болезнью и определить направленность патогенетически обоснованных подходов к терапии с учетом не только вибропротективного эффекта лекарственных препаратов, но и их способности торможения и регресса ремоделирования миокарда.

Ключевые слова: вибрация; ремоделирование миокарда; прогипертрофические транскрипционные факторы; биомаркеры метаболизма коллагена; металлопротеиназы.

Как цитировать

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ЭКО•ВЕКТОР

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INTRODUCTION

V. Dzau and E. Braunwald [1] generalized the data on the morphological and functional changes in the myocardium after myocardial infarction, introducing the concept of "cardiovascular continuum." This concept encompasses a continuous chain of interrelated changes in the cardiovascular system, proceeding according to common patterns and terminal heart damage, such as heart failure. In recent studies devoted to various cardiac pathologies, including arrhythmias, chronic heart failure, arterial hypertension, and post-infarction cardiosclerosis, the term cardiac "remodeling" has emerged. This term encompasses a complex of changes in the size, shape, structure, and biochemical and functional properties of the myocardium under the influence of various risk factors, including vibration.

Accumulated data on the functional state of the heart in patients with vibration syndrome (VS) [2] led to the conclusion that pathophysiological myocardial remodeling is caused by prolonged vibration exposure [3, 4]. The effect of vibration energy, both direct and mediated through neurohumoral factors, leads to the disruption of the structural organization of myocardial fibers [5]. These findings necessitate the implementation of pathogenetically justified therapeutic approaches, which consider the vibration-protective effects of drugs, and the inhibition and reversal of myocardial remodeling to reduce disability and mortality in patients with VS [6].

PATHOPHYSIOLOGICAL PREREQUISITES OF MYOCARDIAL REMODELING UNDER VIBRATION EXPOSURE

All organelles and cells act as ultrastructural targets of vibration. However, membranes and the mitochondria are the most sensitive, and their impairment is manifested as vibration-mediated cytopathies, membranopathies, and mitochondrial dysfunction, which leads to chronic hypoxia [7, 8]. The hypoxia factor plays a pivotal role in the pathogenetic, morphological, and electrophysiological concepts of myocardial remodeling, which is accompanied by impaired metabolism and structure of cardiomyocytes [11].

The prerequisites for maintaining the integrity of cellular and subcellular structures include the efficiency of biochemical reactions and constant reactions of lipid peroxidation and antioxidant defense, which are disturbed in VS [12–14] and negatively affect homeostasis [13, 15].

In addition to direct damage, vibration-mediated changes are predominantly on neurohumoral [8, 16–19] and neuroreflex [20, 21] disorders, which aggravate tissue hypoxia [7]. These changes are mediated by the activation of the prooxidant system. Patients with VS exhibit alterations in calcium homeostasis, which is regulated by glucocorticoids, somatotropin, calcium-regulating hormones (parathormone and calcitonin), and vitamin D [22].

Phase reactions of the hypothalamic–pituitary–adrenocortical, adrenogonadal, and thyroid systems in response to stressful vibration exposure are consistent with the stages of general adaptation syndrome [23]. Furthermore, these systems, which are responsible for inclusion and adaptation, are damaged, as evidenced by experimental studies of the morphofunctional changes in the pituitary and adrenal glands [24]. Vibration-mediated circulatory disorders can cause severe destruction and paranecrosis [25]. Nerve trophic disturbances caused by the pathologic involvement of the central and peripheral nervous systems in response to vibration play an important role. Among the earliest disorders were those affecting the cardiac nerve plexuses. Studies have proven the role of neuroautoimmune integration in the pathogenesis of VS [20, 26, 27].

Hydrodynamic forces generated by vibration cause fluctuations in the central and peripheral intravascular pressure and changes in myocardial blood filling and cardiac output, peripheral blood and lymph flow, and pre- and postload on the myocardium. Subsequent increases in the total peripheral resistance of arteries and arterioles result in significant changes in the ultrastructure of muscle layer cells and degradation of the neurohumoral regulation of their tone [25]. Consequently, pathophysiological factors result in a complex of structural, morphological, metabolic, electrophysiological, and bioenergetic changes, which trigger pathological structural rearrangement (remodeling) of the myocardium in VS.

MORPHOHISTOLOGICAL BASIS OF MYOCARDIAL STRUCTURAL REMODELING

The cardiomyocytes are the primary morphofunctional units in remodeling. Along with subcellular structures (nucleus, mitochondria, ribosomes, and lysosomes), specific proteins (myoglobin, enzymes of glycolysis, tissue respiration, calmodulin, and calsequestrin) are localized in the sarcoplasm of cardiomyocytes. Myofibrillar contractile proteins include myosin, actin, tropomyosin, and troponin. Myosin is the basis of thick filaments, whereas actin, tropomyosin, and troponin are components of thin filaments. These proteins can reversibly bind to calcium ions and ensure the development of geometrically complex active mechanical stresses and deformations in the walls of heart chambers.

Alpha-actinin enters the Z-line of the sarcomere and stabilizes the thin filaments, which are regulated in length by beta-actinin. The fixation and length of thick filaments are associated with special proteins such as

MD and CD, which mediate the fast and slow responses of active mechanical tension to changes in muscle length, and relaxation. Desmin is located between the Z-lines of neighboring myofibrils, ensuring the uniform boundaries of all sarcomeres. In the muscle fiber, the mitochondria are arranged in chains along myofibrils, closely adhering to the membranes of the reticulum. In mature myocardium, the functional activity of the cardiac beta myosin heavy chain with low adenosine triphosphatase activity is predominant.

Each myofibril is encircled by components of the sarcoplasmic reticulum, which physically separates the pathways for various biochemical reactions. This system is composed of a network of longitudinal and transverse tubes, membranes, and vesicles within the sarcoplasm. Compared with atrial working myocytes, ventricular cardiomyocytes are larger (25 μm in diameter and up to 140 μm in length) and more functionally loaded. Consequently, they have a well-developed system of T-tubules, which is involved in wave propagation during electrophysiological excitation from the outer membrane of the fiber to its inner zones and vesicles and cisterns of the sarcoplasmic reticulum. The membranes of the vesicles near myofibrils contain proteins, particularly calsequestrin, which bind Ca^{2+} ions.

In the plasma membrane of cardiomyocytes, all major ionic currents that ensure the phases of the cardiac action potential (Na^+, K^+, and Ca^{2+} currents) are fixed. Among the six Ca^{2+} channels (L, N, P, Q, R, and T), L- and T-type potential-directed channels bore the greatest functional load, which are activated upon membrane depolarization. A review devoted to the biochemical mechanisms of the energy-protective action of blockers of slow high-threshold L-type calcium channels presents the diversity of the structure and functions of calcium channels [22].

The free calcium levels in the cardiomyocyte cytoplasm are regulated by specific proteins, including stromal interaction molecule, sarco(endo)plasmic reticulum $Ca^{(2+)}$-ATPase (SERCA], inositol 1,4,5-triphosphate receptor, Orai (calcium release-activated channel-forming protein), and canonical transient receptor potential channels [28]. The sarcolemmal Ca^{2+}-ATPase, mitochondrial calcium uniport, and sarcolemmal Na^+/Ca^{2+} exchanger are actively involved in the regulation of cardiomyocyte energy potential and control of the actin–myosin system interaction. Actin and myosin are responsible for the contractile functions. Tropomyosin and troponins (I, C, and T) are involved in major regulatory functions. Myomesin; creatine kinase; proteins M, C, F, H, and I; actinins a, b, and g; filamin; and patatropomyosin are responsible for the minor regulatory functions of the muscle.

A study on heart biopsy material from patients undergoing aortocoronary bypass surgery assessed the expression levels of Ca^{2+}-ATPase of sarcoplasmic/endoplasmic reticulum, activity of succinate dehydrogenase and lactate dehydrogenase, and intensity of oxidative phosphorylation processes [17]. The development of heart failure in patients with coronary heart disease and type 2 diabetes mellitus, which is a result of myocardial remodeling, causes the reduced expression of Ca^{2+}-ATPase (*SERCA2a*) and, consequently, a decline in the calcium-depositing capabilities of cardiomyocytes [17]. In remodeling processes, the energy supply of the tissue [30, 31] and dysfunction of ryanodine receptors [32] indicate the functional activity of the sarcoplasmic reticulum Ca^{2+}-ATPase.

The systematic arrangement of cardiomyocyte myofibrils causes the transverse striation of the myocardium. Cell boundaries are formed by insertion disks, which are plasma membranes of two neighboring cardiomyocytes. These disks contain desmosomes, which enables the fixation of cells and myofibrils into nexuses, which are areas of close contact with low electrical resistance. The majority of cardiac muscles in the atrial and ventricular walls are composed of typical cardiomyocytes, providing contractile activity. However, atrial cardiomyocytes, primarily those found in the right atrium, can secrete natriuretic peptides. These peptides have become the topic of pharmacological intervention with the modern combination drug sacubitril/valsartan.

The muscle layers in the ventricular wall spiral around the cavity; thus, the cell arrangement in the heart muscle is close to tangential, creating the least energy-intensive geometric configuration of heart cavities [33]. Modeling the function of the most functionally loaded left ventricle allows the creation of a mechanical block of the mathematical model of its operation, based on the model of myocardial mechanics. In this model, the myocardium is considered a transversely isotropic, incompressible, continuous medium in which passive and active stresses occur in response to deformation, caused by intracellular mechanochemical processes. This model offers the connection between macroscopic (stress and strain) and microscopic (chemical concentrations and mechanical displacements of contractile proteins) quantities [34].

The physical (strain and deformation) and biochemical (calcium ion concentration) parameters of cardiomyocyte functioning may be disturbed by various pathological factors. Regardless of the etiological factor, myocardial cell hypertrophy and polyploidization represent a compensatory mechanism that helps the heart to adapt to new hemodynamic conditions of functioning. In vibration exposure, evidence demonstrates the occurrence of cardiomyocyte hypertrophy in the absence of hypertension and atherosclerotic occlusion of coronary vessels [24, 35]. The assessment of myocardial hypertrophy typically reveals an increase in cardiomyocyte diameter. However, evidence also indicates a correlation between the growth of hypertrophied cells and ventricular dilatation [36].

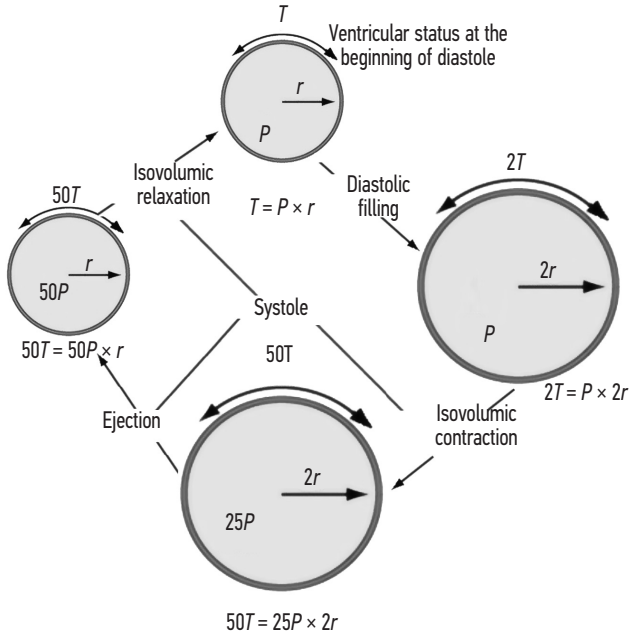

Fig. 1. Relationship between alterations in cardiomyocyte length and tension, ventricular pressure, and volume (radius) during the cardiac cycle according to Laplace's law (according to [37]). *P* — ventricle pressure; *r* — radius of the ventricle; *T* —myocardial wall tension

Рис. 1. Взаимосвязь изменений длины и напряжения кардиомиоцитов, давления в желудочке и его объема (радиуса) во время сердечного цикла в соответствии с законом Лапласа (по: [37]). *P* — давление в желудочке; *r* — радиус желудочка; *T* — общее напряжение стенки желудочка

Considering the outcomes of vibration exposure, which depends on the physical characteristics (frequency, amplitude, acceleration, and exposure vector), structural myocardial materials (actin and myosin proteins and titin protein) are arranged in accordance with certain laws, particularly the Laplace law (Fig. 1).

If the shape of the geometrical model of the ventricle is cylindrical, with the change in ventricular volume being solely dependent on the change in the radius, the total ventricular wall stress per unit wall length along the cylinder axis can be inferred as a function of both the intraventricular pressure (P) and ventricular internal radius (r). This relationship can be expressed by the equation $T = P \times r$ [36]. Consequently, the systolic stress of the ventricular wall [37, 38] is directly proportional to the blood pressure and radius of the cavity and inversely proportional to ventricular wall thickness. As the ventricular volume increases, each cardiomyocyte must generate greater force to achieve a given intraventricular pressure. Ventricular wall thickening helps normalize systolic stress by compensating for an increase in blood pressure or cavity volume. However, under prolonged hemodynamic stresses, cell hypertrophy, reflecting the adaptation at the histological level, is replaced by an unbalanced expansion of the ventricular cavity. This results in increased ventricular cavity radius-to-wall thickness ratio and disturbance in the ideal relationship between the spatial configuration of cardiac cavities, ability to contract, and provision of energy.

Ventricular wall thickening in hypertrophied hearts may be attributed to an enlargement of the cardiomyocyte diameter, whereas ventricular expansion may result from myocardial contractile cell growth [39]. In the compensatory stage of concentric myocardial hypertrophy, the cells predominantly increase their transverse size (diameter). Conversely, in the dilated ventricle at the decompensation stage, cardiomyocytes grow predominantly in length [40].

Studies have examined the pathomorphological rearrangement of various tissues under ischemia exposure in various models. These studies have demonstrated the dynamics of morphometric parameters [41], which objectify experimental data of functioning. A purposeful analysis of morphometric parameters of cardiomyocytes in the case of low-frequency vibration (8 Hz) during 56 sessions of exposure revealed that cell nuclei diameter and length, as well as cell thickness, increased (Table 1). Correlations have been demonstrated among the average diameter of cardiomyocyte nuclei, cell nucleus size, left ventricular (LV) myocardial mass, and myocardial stress [36]. However, a study confirmed an inversely proportional relationship between increased LV mass and contractile activity [36].

The increase in cardiomyocyte diameter occurs in parallel with the increase in the size of nuclei and outpaces the increase in cell length because the cell length only later reaches the level corresponding to the increased size of the nucleus and diameter. Consequently,

Table 1. Morphometric parameters of cardiomyocytes after exposure to 7 and 56 sessions of vibration at a frequency of 8 Hz (as per Vorobyova V.V., Shabanov P.D., 2015 [24])

Таблица 1. Морфометрические показатели кардиомиоцитов на фоне воздействия 7 и 56 сеансов вибрации с частотой 8 Гц (по: Воробьева В.В., Шабанов П.Д., 2015 [24])

Morphometric indices	7 sessions of 8 Hz vibration	56 sessions of 8 Hz vibration
Diameter of the cardiomyocyte nucleus with signs of swelling, μm	3.61	5.66*
Length of the cardiomyocyte nucleus with signs of swelling, μm	8.83	12.67*
Diameter of the nucleus with dense arrangement of chromatins, μm	2.57	4.66*
Length of the nucleus with dense arrangement of chromatins, μm	8.23	11.82*
Cell thickness with dense cytoplasm without dystrophy, μm	8.07	12.67*

*$p < 0.05$ compared with the group of 7 sessions of 8 Hz vibration.

the morphohistological stages of compensatory and adaptive changes at the myocardial structural and functional levels are completed [36]. The upper limit of the cell diameter increases during the development of hypertrophy is likely caused by the deviation of the volumetric (proportional to r^3) and surface (proportional to r^2) characteristics from the optimal values [39]. Different mechanisms are assumed to be involved in the changes in cell diameter and length. For instance, the diameter is directly correlated with the diameter of cell nuclei, and the length increases as the zones of myofibril loss expand [36].

Hypertrophic cells demonstrate pathomorphologic rearrangement with myofibril loss once their transverse growth is completed. The loss of myofibrils suggests the transition of myocardial hypertrophy to the decompensation stage and the formation of degenerative (dystrophic) features in cells, particularly the loss of sarcomeres [42]. Concurrently, the general structures of these cells increased [36], and embryonic genes are reactivated [43], which indicate an adaptive reorganization of cellular material accompanied by a weakening of tissue-specific features [15, 36]. The fundamental objective of such an adaptation strategy at the structural level of myocardial tissues is to reduce the contractile function of cells and consequently the energy deficit. However, this inevitably results in reduced contractile activity of the LV, increased myocardial systolic stress, and heart failure.

Changes in the shape and increases in the volume of the heart chambers occur to maintain the cardiac output under pathological conditions. This phenomenon induces oxidative phosphorylation to provide energy to the actin–myosin system. However, hypoxic cellular metabolism and bioenergetic hypoxia formed under vibration exposure inhibit the full supply of energy to the tissue [7]. A vibration-mediated hypoxic (ischemic) state has deleterious effects on the pathological structural reorganization of the myocardium, reducing tissue resistance to hemodynamic loads, accelerating the transformation of the size and geometry of cardiac cavities, and worsening systolic and diastolic functions, primarily of the left ventricle. Furthermore, it increases the risk of arrhythmias [44].

MYOCARDIAL REMODELING AND CARDIAC PLASTICITY CONTROL SYSTEM

Myocardial stroma proteins are represented by collagen and elastin, whereas cytoskeleton proteins include taitin 1, taitin 2, nebulin, vinculin, desmin (skeletonin), vimentin, synemin, Z-protein, Z-nin, and dystrophin. The equilibrium between the synthesis and breakdown of collagen prevents the development of fibrosis in the extracellular matrix. To understand the pathological structural (morphological) and energetic rearrangement of tissues under the influence of hemodynamic and ischemic factors, the involvement of numerous mediators that regulate the metabolism, proliferation, growth, and cell survival must be considered (Table 2).

The following enzymes have been demonstrated to participate in the remodeling process: phosphatidylinositol 3-kinase and protein kinase B-alpha (product of *AKT1*), mammalian target of rapamycin complex 1, mitogen-activated kinases ERK1/2 (extracellular signal-regulated kinase 1/2), and AMP-activated protein kinase [45]. The intracellular transmitter inositol 1,4,5-trisphosphate (IP3-R), which is embedded in the nuclear membrane, modulates the transmembrane current of Ca^{2+} ions in two ways. First, it protects the cardiomyocyte nucleus from ion overload during systole. Second, it regulates the activity of different families of transcription factors, including myocyte enhancer factor 2 (Mef2) and nuclear factor of activated T cells (NFAT) [46, 47].

The NFAT family of transcription factors, which includes NFATc1-c4 and NFAT5, participate in maintaining calcium homeostasis in cardiomyocytes and regulating the transcription of genes that express growth factors [46]. A diverse family of MEF2 transcription factors (Mef2a, Mef2b, Mef2c, and Mef2d) acts as key regulators of cardiac gene expression [48].

Table 2. Factors regulating the mRNA synthesis rate on DNA matrix by binding to specific DNA sites (signal-dependent transcription factors) to control cardiac nutrition and plasticity

Таблица 2. Факторы, регулирующие скорость синтеза мРНК на матрице ДНК путем связывания со специфическими участками ДНК (сигнал-зависимые транскрипционные факторы) контроля сердечной трофики и пластичности

Factors	Roles
Activation protein 1 (AR 1) consists of homodimers or heterodimeric complexes of Fos (c-Fos, FosB, Fra1, and Fra2), Jun (c-Jun, JunB, and JunD), activating transcription factor subfamilies (ATFa, ATF 2, and ATF 3), and Jun dimerization proteins (JDP 1 and JDP 2). It was discovered by W. Lee et al. in 1987	A transcription factor, which is specific to a particular DNA sequence, is a target for compounds that induce cell proliferation or differentiation. It is crucial in the regulation of gene expression of proinflammatory cytokines, chemokines, adhesion molecules, matrix metalloproteases, and immune response genes. It participates in cell growth, differentiation, and apoptosis
Nnuclear factor κB (NF-κB) family includes five proteins: NF-κB1, ReLA, NF-κB2, RelB, and c-ReL (NF-κB2, RelB, and c-ReL are found only in lymphocytes and lymphatic tissue cells). It was identified by R. Sen and D. Baltimor in 1986	It controls the expression of genes related to immune response, inflammation, apoptosis, and cell cycle (p53, cyclin D1, fibroblast growth factors, and platelet-derived growth factors)
Myocyte enchancer factor 2 (MEF2) is a muscle-specific transcription factor of the MADS box class. It was discovered by N.J. Brand in 1997	This prohypertrophic transcription factor is involved in the control of cardiac myocyte proliferation and differentiation of resident cardiac stem cells in CMCs
Serum response factor (SRF) is a serum-sensitive activator of the *c-fos* gene promoter. It was identified in 1988	SRF is classified as a MADS box class transcription factor, one of the key nuclear targets for signaling regulation of cell growth, differentiation, and transformation, and binds to a serum response element in the promoter region of target genes. It is a prohypertrophic factor
GATA4 is a transcription factor that includes six transcription factors (GATA 1–6) containing a common DNA fragment and a zinc-containing end domain. It was first analyzed and identified by G. Caramori et al. in 2001	It is a prohypertrophic transcription factor that regulates genes encoding proteins critical for differentiation (including stem cells into the cardiomyocytes in the presence of Baf60c protein) and function of CMCs, particularly troponin C, alpha-myosin heavy chain, and brain natriuretic peptide
Nuclear factor of activated T cells (NFAT) is a nuclear factor of activated T cells and represented by NFATc1-c4 and NFAT5. It was identified by A. Rao et al. in 1997	NFAT is involved in the regulation of the immune system, maintenance of calcium homeostasis in CMCs, and growth and proliferation of CMCs. It acts as a prohypertrophic transcription factor
cAMP response element-binding protein (CREB) is a cAMP-dependent transcription factor. It was first identified by M.R. Montminy and L.M. Bilezikjian in 1987	CREB is a resident nuclear factor that regulates somatostatin, c-fos, zif 268, peptide antioxidant (Trx1, SOD1), and Bcl 2 family antiapoptotic factor genes
p53 protein is a transcription factor that regulates the cell cycle. It was identified by D.P. Lane in 1990	Upon activation, it arrests the cell cycle, and DNA replication occurs. Strong stress signaling triggers apoptosis
Downstream regulatory element antagonist modulator (DREAM) is a transcription repressor that suppresses the transcriptional activity of cell cycle-related genes in the dormant state. It was discovered by A.M. Carrion et al. in 1998	As a modulator antagonist of downstream regulatory elements, DREAM suppresses the transcriptional activity of genes associated with the cell cycle in the resting state

Note. CMC, cardiomyocyte

Sigma receptors of the σ1-R subtype are expressed not only in the neurons of the cerebral cortex, striatum, and hippocampus but also in thoracic aortic cells and cardiomyocytes. This expression exerts intranuclear control over the gene expression of the antiapoptotic protein Bcl 2 by the activation of the nuclear transcription factor kappa-B (NF-κB) [49, 50]. In the context of myocardial reperfusion injury, activated σ1-R receptors suppress cardiomyocyte apoptosis by reducing the levels of gene expression of proapoptotic protein *Bax* and caspase 3. This effect was considered caused by the activation of the σ1-R PI3K/Akt/eNOS signaling pathway [51].

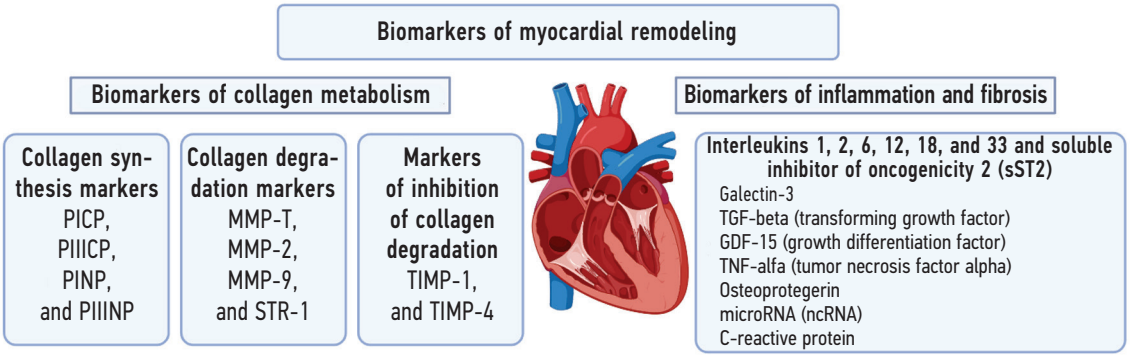

Fig. 2. Biomarkers associated with myocardial remodeling. PCP and PNP — carboxy and aminopropeptides of procollagen; MMP — metalloproteinases; TIMP — tissue inhibitors of metalloproteinases; CTP-1 — C-telopeptide of type I collagen
Рис. 2. Некоторые биомаркеры ремоделирования миокарда. PCP и PNP — карбокси- и аминопропептиды проколлагена; MMP (ММП) — матриксные металлопротеиназы; TIMP (ТИМП-1) — тканевые ингибиторы матриксных металлопротеиназ; CTP-1 — С-телопептид коллагена I

The functioning of gene network components and molecular genetic systems that provide gene expression control in cardiomyocytes is associated with the control system of "cardiac plasticity" and endogenous collagenolysis. Biomarkers of collagen metabolism can be classified as follows (Fig. 2).

Extracellular matrix degradation, which includes matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), is one of the most crucial links in the remodeling of target organs [52–55]. This system can be assessed in clinical conditions by solid-phase enzyme immunoassay using standard test kits [56], which allows for the measurement of MMP 9 and TIMP 1. Collagen and other components of the extracellular matrix [57] activate proinflammatory and profibrotic factors. In addition, a high MMP activity has been linked to the progression of myocardial fibrosis [53, 54, 58–60]. The following transcription factors act as regulators of the concentration and interaction of MMPs and their inhibitors: nuclear factor κB, activator protein 1, heparin-binding endothelial growth factor, T cell growth factor, and others [61].

Serum markers of collagen synthesis, such as carboxyterminal propeptide of types I and III (PICP and PIIICP, respectively) and aminoterminal propeptide of procollagen types I and III (PINR and PIIINR, respectively), indicate that collagen synthesis is more prevalent than its degradation in the extracellular matrix. This process results in the degradation of extracellular matrix components, activation of proinflammatory and profibrotic factors, progression of myocardial fibrosis [55, 57, 61], and an increase in diastolic myocardial stiffness, which leads to impaired intracardiac hemodynamics and electrophysiological, diastolic, and systolic dysfunction [62].

Some studies have demonstrated high fibrotic tissue formation activity, with the increase in extracellular matrix space reaching significant differences (8 times) compared with normal [56]. This has been linked to a high risk of sudden cardiac death in young patients with hypertrophic cardiomyopathy [56] and end-stage heart failure in older patients [63].

A review of the literature on the state of signal-dependent transcription factors of cardiac plasticity control in VS reveals only limited information, often indirect, on the levels of proinflammatory cytokines [18, 26]. A study reported the carriage of the rs3834129 polymorphism of *CASPS*, which is a marker associated with resistance to VS formation and with a low level of activity of fibroplastic processes involved in remodeling [64]. The carriage of specific alleles of G894T of the endothelial dysfunction gene is associated with an increased risk of developing cardiovascular diseases, including those associated with metabolic syndrome and vibration exposure [65]. However, data on vibration-mediated structural and functional myocardial disorders in experimental and clinical studies have not been systematically analyzed, and the underlying mechanisms of remodeling, such as endothelial, oxidative and metabolic, and immunoinflammatory mechanisms, have not been fully elucidated.

SIGNS OF STRUCTURAL MYOCARDIAL REMODELING ACCORDING TO ECHOCARDIOLOGIC STUDIES

Cardiomyocyte hypertrophy resulting from vibration-mediated stressing effects is the consequence of several hemodynamic (pressure and volume overload, vascular wall stiffness, blood viscosity, heart rhythm disturbance) and non-hemodynamic (neurohumoral activation, genetic predisposition, hypoxia, and decreased activity of energy metabolism) causes [16]. In parallel, structural disorders of peripheral vessels include thickening of the medial layer of their wall, reduction of the lumen, and endothelial dysfunction [25].

Diagnostic methods such as two-dimensional echocardiography (Echo-CG), magnetic resonance imaging, and radionuclide ventriculography are employed to ascertain LV dimensions, volume, and contractile activity.

Stress Echo-CG with dobutamine and dipyridamole, myocardial scintigraphy, magnetic resonance imaging, and positron emission tomography have been used to evaluate myocardial viability. To assess the viability of cardiac muscle tissue, radiopharmacological agents, such as ^{199}TlCl and ^{201}TlCl, are employed as markers of membrane ATPase of cardiomyocytes [66].

The complex assessment of cardiac activity performed under ultrasound guidance yielded data on the cardiac condition of patients with grade I and II VS [3]. These data indicated a moderate increase in LV myocardial mass, LV myocardial mass index with increasing total LV volume, and myocardial volume under increased systolic intraventricular pressure. These findings reflect the presence of LV dysfunction, and a predominant variant is a relatively stable compensation to long-term dysfunction with moderate myocardial hypertrophy.

In Table 3, the informativeness and prognostic significance of the parameters have high statistical significance. It is evidenced by the association of increased LV end-systolic and end-diastolic volume with decreased ejection fraction and development of severe heart failure, embolic stroke, risk of repeated infarction, and sudden cardiovascular death.

The myocardium of patients with VS exhibits an increase in LV stress and tension in the diastolic phase in both the annular and meridional directions. The increase in myocardial mass reduces the stress on the cardiac wall; however, this leads to a decrease in the intensity of work of cardiac structures compared with healthy ones by 1.2 times ($p < 0.05$) because of the removal of a part of the load per unit of cardiac mass (Table 3). This results in the disruption of LV myocardial geometry and mass, which manifests as concentric remodeling of the left ventricle. These changes create prerequisites for LV diastolic function disturbance, as evidenced by the E/A ratio, i.e., the ratio between LV filling in diastole (peak E) and atrial systole (peak A) [56]. Membrane and ionic disturbances, which depend on the substrate and energy supply of cardiomyocytes, are the basis of such Echo-CG functional disorders [22].

The analysis of the mechanical activity of the right ventricle indicates that the right ventricle tension period has been prolonged (by 20 % in patients with grade I VS). This is associated with a significant increase in pulmonary artery pressure (by 39.9 %) and increased afterload for the right ventricle by 1.8 times. Undoubtedly, the hypoxic type of metabolism, hypercalcemia, and hypercalciuria [22], which are hallmarks of the pathological physiology of VS, disrupt the electrophysiological characteristics of cells within the cardiac conducting system and cardiomyocytes.

In patients with grade II VS caused by the morphofunctional reorganization of the heart, energy consumption per contraction increases by 1.2 times. This increase corresponds not only to the deterioration of myocardial diastolic function (decrease in diastolic reserve) but also to the deterioration of LV contractile function (pumping function of the heart). Furthermore, even in the post-contraction period, hypertrophy progresses further [4], which represents an extremely unfavorable factor. LV hypertrophy is an independent risk factor for sudden cardiac death, myocardial infarction, heart failure, ventricular arrhythmias, and a significant increase in total mortality and mortality from cardiovascular causes.

Table 3. Functional state of the left ventricle in patients with stage I vibration disease in comparison with healthy individuals, $M \pm \delta$

Таблица 3. Некоторые показатели функционального состояния левого желудочка у пациентов с вибрационной болезнью I степени в сравнении со здоровыми людьми, $M \pm \delta$

Indicators	Healthy individuals	Patients with stage I vibration syndrome
Total volume, mL	207.08 ± 30.07	238.86 ± 31.94*
Myocardial mass, g	107.7 ± 16.6	131.6 ± 15.7*
Myocardial mass index, g/m^2	67.6 ± 10.9	75.6 ± 7.8*
Systolic intraventricular pressure, dyne/cm^2	109.2 ± 14.4	125.5 ± 23.1*
Intramyocardial meridional diastolic stress, dyne/cm^2	47.2 ± 5.4	103.0 ± 15.5*
Circulating intramyocardial systolic stress, dyne/cm^2	91.2 ± 12.0	217.9 ± 44.8*
End-diastolic pressure, mm Hg	8.9 ± 1.1	10.1 ± 1.3*
Average posterior wall relaxation rate, cm/s	6.3 ± 1.4	4.1 ± 1.0
Ratio of early and atrial filling velocities	1.5 ± 0.3	1.3 ± 0.2
Early atrial filling phase, s	0.15 ± 0.03	0.19 ± 0.03

*Differences are statistically significant at $p < 0.05$ (data from Tretiakov S.V. et al., 2003 [3])

CONCLUSIONS

Many myocardial diseases are caused by the functional, morphological, and electrophysiological transformation of cardiomyocytes and the extracellular matrix. Cardiomyocyte hypertrophy and the increase in the size of the cell nucleus are accompanied by a gradual loss of myofibrils. This occurs only at a certain stage of adaptation, preventing energy deficiency in cells. Nevertheless, the compensatory–adaptive changes in cardiomyocytes that occur in response to stressful physical, hemodynamic, neurohumoral, and bioenergetic stimuli inevitably result in maladaptation, uncontrolled apoptosis, and tissue necrosis [24]. Cardiomyocyte damage is accompanied by impaired tissue plasticity, manifested as the activation of collagen and other extracellular matrix components. This symbolizes the structural and functional multidimensionality of the remodeling process.

Accumulated data on remodeling mechanisms enrich the theoretical direction of research and open the door to their applied use. This includes the assessment of the ratios of MMPs and TIMPs and levels of proinflammatory cytokines, tumor necrosis factor-α, and interleukin-1. Cardiac magnetic resonance imaging has enabled the detection of areas of delayed gadolinium chelate salt accumulation (late gadolinium enhancement), which has led to the identification of pathological accumulations of collagen. Furthermore, T1 mapping has been employed to assess the severity of myocardial interstitial fibrosis. Strain elastography can be used to measure myocardial elasticity and indirectly assess collagen and elastin components of the extracellular matrix. A special type of modern echocardiography can track the trajectory of myocardial acoustic markers during the cardiac cycle, acquire digital values, and make a conclusion about global and regional LV deformation in longitudinal, circular, and radial directions [57].

In addition to the previously identified biomarkers, namely, troponin I, C-reactive protein, brain natriuretic peptide, creatine phosphokinase, and alkaline phosphatase), new biomarkers such as MMP, galectin 3, GDF15, sST2, and microRNAs, are beginning to be identified, which indicate inflammation, impaired immune response, tissue degeneration, and fibrosis with remodeling leading to chronic congestive heart failure [58, 59]. The rates of collagen I and collagen III synthesis can be determined based on circulating biomarkers PICP, PIIINP, and C-terminal telopeptide. This suggests the dependence of the expression of different collagen isoforms on etiologic factors.

A review of the literature on myocardial remodeling processes in patients with VS reveals the paucity of systematic data on structural and functional myocardial disorders in experimental and clinical studies. Furthermore, information on the systemic remodeling mechanisms, including endothelial, oxidative and metabolic, and immunoinflammatory mechanisms, is limited. In addition, changes in adrenomedullin, atrial natriuretic peptide system, regulating the pathological activation of the renin–angiotensin–aldosterone system, and sympathetic section of the autonomic nervous system have not been studied. In-depth knowledge about vibration-mediated pathology has implications for the development and introduction of new research methods in occupational pathology. It also has implications for the pharmacological effects of drugs that can inhibit and cause regression of the structural remodeling of myocardium and vessels, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers in combination with neprilysin inhibitors [67–71], calcium channel blockers [72], and oral hypoglycemic agents [73, 74].

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. The contribution of each author: V.V. Vorobieva, O.S. Levchenkova, K.V. Lenskaya — manuscript drafting, writing and pilot data analyses; P.D. Shabanov — paper reconceptualization and general concept discussion.

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