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Research Article

Role of bioenergetic hypoxia in the morphological transformation of the myocardium during vibration disease

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ABSTRACT

BACKGROUND: Analysis of literature on the structural changes in the heart in patients with vibration disease using echocardiographic research methods revealed a concentric type of remodeling of the left ventricular chambers, which is associated with a high risk of cardiovascular complications, including sudden cardiac death, in people of working age.
AIM: To determine the role of bioenergetic hypoxia in the development of morphological transformation of the myocardium to substantiate the efficacy of pharmacotherapy for vibration disease.
MATERIALS AND METHODS: The energy production activity of cellular systems of heart tissue in vitro was analyzed by the polarographic method using a closed galvanic-type oxygen sensor (Clark electrode). The stressful effects of vibration were confirmed by the dynamics of the morphohistological picture of changes in the myocardial tissue of the left ventricle in the apical region after standard alcohol–paraffin wiring and staining of histological preparations with hematoxylin and eosin.
RESULTS: Evaluation of the morphometric and bioenergetic parameters of cardiomyocytes under various experimental vibration modes (7, 21, and 56 sessions with a frequency of 8 and 44 Hz) confirmed the relationship between the provision of tissue with energy potential and morphological signs of pathological structural changes in the myocardial tissue, such as hypertrophy of cardiomyocytes, development of fibrosis, restructuring of the vascular bed, and necrosis.
CONCLUSION: Analysis of the relationship between energy metabolism and morphohistological transformation of heart tissue allows us to resolve the role of universal and specific mechanisms in cardiac remodeling in the presence of vibration and pathogenetically substantiate the choice of drugs that not only have a vibration-protective effect but also inhibit pathological structural changes in the myocardial tissue.

Keywords: vibration; hypoxia; energy metabolism; hypertrophy and fibrosis of cardiomyocytes; myocardial remodeling.

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Научная статья

Роль биоэнергетической гипоксии в морфологической трансформации миокарда при вибрационной болезни

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АННОТАЦИЯ

Актуальность. Анализ литературных источников, посвященных изучению структурных изменений со стороны сердца у больных вибрационной болезнью с помощью эхокардиографических методов исследования, выявил концентрический тип ремоделирования камер левого желудочка, ассоциированный с высоким риском сердечно-сосудистых осложнений, в том числе внезапной кардиальной смерти у лиц трудоспособного возраста.

Цель — определить роль биоэнергетической гипоксии в развитии морфологической трансформации миокарда для обоснования фармакотерапии вибрационной болезни.

Материалы и методы. Изучение активности энергопродукции клеточных систем ткани сердца *in vitro* проводили полярографическим методом с помощью закрытого кислородного датчика гальванического типа (электрод Кларка). Стрессирующее воздействие вибрации подтверждали динамикой морфогистологической картины изменений ткани миокарда левого желудочка в области верхушки после стандартной спиртово-парафиновой проводки и окраски гистологических препаратов гематоксилином и эозином.

Результаты. Оценка морфометрических и биоэнергетических показателей кардиомиоцитов на фоне различных экспериментальных режимов вибрации (7, 21, 56 сеансов с частотой 8, 44 Гц) подтверждает взаимосвязь между обеспеченностью ткани энергетическим потенциалом и формированием морфологических признаков патологической структурной перестройки в виде гипертрофии кардиомиоцитов, развития фиброза, изменения сосудистого русла, а также некроза.

Заключение. Анализ взаимосвязи энергетического обмена и морфогистологической трансформации ткани сердца позволяет поставить вопрос о роли универсальных и специфических механизмов в ремоделировании сердца на фоне вибрации и патогенетически обосновать выбор лекарственных препаратов, не только обладающих вибропротективным, но и тормозящих патологическую структурную перестройку ткани миокарда, действием.

Ключевые слова: вибрация; гипоксия; энергетический обмен; гипертрофия; фиброз кардиомиоцитов; ремоделирование миокарда.

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ЭКО•ВЕКТОР

BACKGROUND

The significant increase in morbidity and disability caused by occupational vibration results in serious social, economic, and medical problems. Therefore, the pathogenesis of hand–arm vibration syndrome (HAVS) and search for pathogenetic therapy should be further studied [1]. The significance of HAVS is increasing in both medical and social contexts owing to the loss of working capacity among young people employed in industries such as aviation, mining, heavy-duty machine operation, and construction equipment.

Clinical data regarding the functional state of the heart in HAVS patients showed that prolonged exposure to vibration leads to the development of myocardial remodeling processes [2]. Concentric left ventricular hypertrophy is observed in 31.8% of HAVS patients and is associated with the highest risk of cardiovascular complications, including sudden cardiac death, myocardial infarction, heart failure, and ventricular arrhythmias [3–5].

Cardiac tissue undergoes pathological structural rearrangement, called remodeling, which is determined by the structural reorganization and adaptive energy metabolism rearrangement of tissues. The assessment of myocardial condition exposed to experimental [6] and industrial pathological factor vibration [7] is complex. It includes the analysis of energy metabolism and morphohistological transformation of heart tissue. This reveals the role of universal [8] and specific mechanisms in remodeling and confirms the choice of drugs that have a vibration-protective effect and inhibit pathological structural rearrangement of myocardial tissue [9].

MATERIALS AND METHODS

The energy production of cardiac tissue cell systems *in vitro* was analyzed using a polarographic method with a closed galvanic-type oxygen sensor (Clark electrode). The detailed methodology and composition of media for tissue homogenate isolation and incubation were revealed in our previous studies [10].

We analyzed the contribution of FAD- and NAD-dependent links of the respiratory chain (RC) to evaluate changes in the function of mitochondria [11] in heart tissue (specifically the left ventricular apex zone) due to exposure to different modes of vibration. Furthermore, we examined the tissue consistency of changes in energy metabolism during incomplete gradation cycles of metabolic states of mitochondria while oxidizing endogenous and exogenous substrates in a "rest → activity in dissociated state" manner and analyzed dysregulatory and low-energy shifts at the mitochondrial level. The effects of vibration irradiation on other levels of biological integration, such as cellular, tissue, and interorgan, were also assessed.

Moreover, a multifactor analysis was used to implement a systems approach [10]. This enabled the characterization of the interaction process between mitochondrial communities and unfavorable factors by considering all available parameters–responses, while considering the tissue specificity of their functional activity during adaptation to the disturbing factor of vibration [12]. The confirmed effect of vibration on stress was demonstrated through the dynamics of catalase activity in blood plasma and washed erythrocytes, energy status of lymphocytes through succinate dehydrogenase activity, and changes in the morphohistological picture of myocardial tissue [10, 13, 14].

DYSFUNCTION OF BIOENERGETIC APPARATUS AND ISCHEMIC REMODELING OF MYOCARDIAL TISSUE

The myocardium is a highly vulnerable organ owing to its high functional activity and large energy requirements, which are maintained by aerobic processes. Energy metabolism in the myocardium is provided by free fatty acid, glucose, lactic acid, and amino acid metabolism. Beta-oxidation of fatty acids occurs in the mitochondrial matrix under aerobic conditions. The process concludes with $FADH_2$, NAD(H), and acetyl-coenzyme A production. Then, acetyl-coenzyme A enters the tricarboxylic acid cycle as the primary energy source for adenosine triphosphate (ATP) synthesis through oxidative phosphorylation. Under physiological tissue oxygenation conditions, myocardial demands for oxidation substrates are met by fatty acids, which are efficiently oxidized through the high activity of beta-oxybutyrate oxidase. Additionally, myocardial mitochondria oxidize endogenous substrates such as succinic, malic, isolimonic, fumaric, and ketoglutaric acids and amino acids, ketone bodies, and pyruvate in smaller amounts. The functional load level on the heart determines substrate supply. As the functional load increases, the role of beta-oxidation of fatty acids decreases, whereas the activity of aerobic glycolytic processes increases [15].

The myocardium has high energy metabolism and is susceptible to the impacts of stress, hypoxia, and energy deficiency. The heart muscle is required to generate rapid contractions and continuously alternate between periods of contraction and relaxation. This need forces the tissue and organ to modify its structure and spatial configuration according to changing hemodynamic and non-hemodynamic indices, such as pressure and volume overload, stiffness of the vascular wall, blood viscosity, heart rate, hypoxia, neurohumoral activation, genetic predisposition, altered metabolism, and altered energy metabolism [16, 17].

Epidemiologic studies reveal that workers exposed to vibration hazardous conditions for over 10 years have a higher frequency of myocardial pathology compared to other population groups of similar age and gender [2]. This is because of increased activity of the sympathoadrenal system [18, 19], the formation of a hyperkinetic type of blood circulation [20], decreased myocardial contractility in the preparatory phase, diastolic dysfunction of the left and right

ventricles [21], activation of the lipid peroxidation system [22], myocardiodystrophy development with various heart rhythm disturbances recorded on electrocardiogram, and concentric left ventricle hypertrophy [23].

The formation of concentric left ventricular hypertrophy requires intense energy requirements and mobilization of plastic material. This involves parallel or sequential sarcomeres, which are associated with cardiomyocyte dilation or elongation. Experimental studies have shown that hypoxia develops in myocardial tissue due to vibration exposure, regardless of whether it is general or local. This causes NAD·H-oxidase link inhibition, which is the most sensitive to the stressing effect of vibration. At level II of the enzyme-substrate complex (FADH-oxidase), the functional activity of the RC leads to endogenous succinate oxidation. This phenomenon is universal and can be measured, including the summation of vibration effects [6, 13, 14].

The protein factor hypoxia-inducible factor (HIF)-1 plays a significant role in the molecular mechanisms of cell adaptation to stress. Research has shown that HIF-1 functions as a transcription factor during pathological tissue remodeling. This triggers the expression of various HIF-1-dependent target genes and synthesis of protective adaptive proteins [24], which counteract the harmful effects of myocardial stress caused by several factors [25].

Under hypoxic stress, the *IF1 OPA1* cascade stabilizes the structure and activity of the ATP synthetase F_1F_0 dimer, causing mitochondria to function in the supercomplex mode [26]. This is due to the ability of the mitochondrial apparatus of cardiomyocytes to form a reticulum, which is a single system of mitochondria [27, 28]. Mitochondria are connected through intermitochondrial contacts, which are disks 0.1–1 μm in diameter. These contacts react to changes in the organism's physiological status by undergoing restructuring and recombination transformations [29].

The disturbance of calcium metabolism in HAVS patients [30, 31] plays a crucial role in the transformation of RC operation toward clotting factor II activity dominance. This is because calcium channels and Ca^{2+}-regulating mechanisms determine the level of free calcium in the myoplasm and are critical for cardiomyocyte functioning [32]. The calcium entry system components, including calcineurin, protein kinase A, and calcium/calmodulin-dependent kinase II, are functionally coupled and their interdependence is influenced by their redox potential. Moreover, these components are involved in myocardial remodeling mechanisms. Disruption of Ca^{2+} ion delivery to the actin–myosin system of cardiomyocytes and delayed decrease of its concentration during repolarization can lead to impaired muscle relaxation during diastole, called diastolic dysfunction.

Owing to the involvement of several biochemical mediators, such as phosphatidylinositol-3-kinase and protein kinase B alpha (product of *AKT1* gene), mammalian target of rapamycin complex 1, and mitogen-activated kinases extracellular signal-regulated kinase 1/2 and AMP-activated protein kinase, a connection between the regulation of energy metabolism and cell proliferation, growth, and survival and the mechanisms of myocardial structural and geometric reorganization in vibration exists [32, 33]. However, these mechanisms are poorly understood.

MORPHOLOGICAL SIGNS OF ISCHEMIC REMODELING OF MYOCARDIAL TISSUE

Stressful myocardial damage [25] can lead to pathological structural reorganization of the myocardial tissue through molecular and bioenergetic mechanisms. The circulatory system mediates the energy demands of the cell and tissue, which are open thermodynamic systems. The morphofunctional status is regulated by energy supply. From a morphological perspective [34], remodeling involves cardiomyocyte hypertrophy, fibrosis development, vascular channel remodeling, and cardiomyocyte and stromal cell apoptosis.

Experimental studies have shown that the swelling of cardiomyocyte cells and their nuclei with dystrophic changes of zonal character increases general vibrations of different frequencies (8 and 44 Hz) and durations (7, 21, and 56 sessions). Additionally, an increase was noted in the area of dystrophy zones and their spread from subendocardial to intramural sections.

Signs of persistent compensatory hypertrophy were observed in subendocardial myocytes after 56 sessions of 8 Hz stimulation, and signs of hypertrophy combined with dystrophic changes were found after 56 sessions of 44 Hz stimulation [10]. Myocardial hypertrophy aims to reduce stress on the heart wall; however, it can lead to decreased contractile activity, diastolic dysfunction, and changes in the spatial configuration of the myocardium. Echocardiologic studies have shown that these changes are observed in patients with HAVS [21].

Changes in the quantitative ratio of myocardial parenchymal and stromal tissue are the main indicator of remodeling. An increase in stromal cell reaction with inflammatory tissue infiltration was observed in the intercellular substance. The number of histiocytic and lymphocytic cells increased in the myocardial interstitium in vibration sessions 7–21, and their number decreased by session 56. The remodeling process is characterized by changes in the cellular composition, including neutrophilic granulocytes, lymphocytes, and fibroblastic cells. These changes are observed in the pathological structural rearrangement of the myocardium, primarily of ischemic genesis [35].

The full blood perfusion of the heart muscle increased corresponding to the number of vibration sessions. The most intensive increase was observed in sessions 7 to 21. By session 56, signs of blood circulation stabilization were observed, which were confirmed by reduced full blood flow

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Table 1. Pathophysiological manifestations of vibration effects at the cellular and tissue levels
Таблица 1. Патофизиологические проявления вибрационного воздействия на уровне клеточных структур и тканей

Ultrastructural level of exposure	Result of the vibration effect
Mitochondria	Swelling, matrix enlightenment, reaction of cristae, outer and inner membrane destruction , change of shape, and appearance of a large number of small mitochondria (Sarbaeva N.N., 1987)
Tissue respiration	Phase changes in the intensity of oxidative processes and their energy regulation in myocardial tissue and generalized disorders in the conjugating systems of FAD- and NAD-dependent parts of the mitochondrial respiratory chain indicate a low-energy shift in myocardial energy supply (Vorobieva V.V., Mazina N.K., Shabanov P.D., 2007–2014)
Enzymes	Activation of a- and β-receptor-adenylase complex, key enzymes of glycolysis, glycogenolysis, lipolysis, disturbance of carbohydrate-energy metabolism of the myocardium, and accumulation of intermediate underoxidized metabolic products: pyruvic, lactic, and alpha-ketoglutaric acids and changes in total and residual nitrogen, creatine, and creatinine (Gogoleva O.I., Malyutina N.N., 2000; Sukharevskaya T.M. et al., 2000; Vorobieva V.V., Shabanov P.D., 2007–2015; Saarkopel L.M. et al., 2017)
Intermitochondrial interaction	Loss of regulatory function in the mitochondrial-reticular network leads to the transformation of interorgan interrelations and functional activity of mitochondria during adaptation. This transformation happens simultaneously with changes in metabolic pathways and results in mitochondrial dysfunction or bioenergetic hypoxia (Mazina N.K., Vorobieva V.V., 2007; Vorobieva V.V., Shabanov P.D., 2020)
Cellular membranes	Vibration-mediated cytopathies and membranopathies reflected by tissue biomarkers (Ishitake T., 1990; Sukharevskaya T.M. et al., 2000; Saxton I.M., 2000; Kiryakov V.A. et al., 2010)
LPO and AOS systems	The serum chemiluminescence of blood serum of HAVS patients is 3.5 times higher than the physiological level (Balan G.M., Kushelevsky S.G., 1987; Allesio H.M., 1988; Sukharevskaya T.M. et al., 2000; Vorobieva V.V., Shabanov P.D., 2015; Malyutina N.N. et al., 2019)
Calcium homeostasis	Violation of calcium homeostasis due to decreased calcium-binding capacity of blood serum, decreased renal clearance of calcium, and increased serum total and especially ionized calcium; formation of the "calcium triad" in HAVS (Kolomiets V.V., Merzon A.K., 1985; Kolomiets V.V., 1987; Kostyuk I.F., Kapustnik V.A., 2004; Vorobieva V.V., Levchenkova O.S., Shabanov P.D., 2023)
Hypoxia and hypoxemia	Venous hyperoxia, reduction of arterio-venous oxygen difference, and oxygen utilization by tissues in HAVS patients. Hypoxia and hypoxemia induce a complex of structural, morphological, and metabolic changes, culminating in dystrophic rearrangements by vibration visceropathy (Okada A. et al., 1987; Sukharevskaya T.M. et al., 2000, Saxton J.M, 2000; Vorobieva V.V., Shabanov P.D., 2009, 2015)

Note: AOS — antioxidant system; HAVS — hand–arm vibration syndrome; LPO — lipid peroxidation.
Примечание: АОС — антиоксидантная система; ВБ — вибрационная болезнь; ПОЛ — перекисное окисление липидов.

in the venules and decreased diapedesis hemorrhages. The degree of arterial wall edema increased with the vibration dose. Microangiopathies were manifested by edema of vessel walls, their spasm, and rarefaction of arteriolar and capillary network, indirectly indicating dysadaptation with decreased pumping function of the left ventricle. After high-frequency prolonged vibration, swollen endothelium with hyperchromic nuclei is observed in the myocardial capillaries; the system of hollow venules and capillaries is pronounced, arteriolar network is sparse, and architectonics of blood vessels is sharply changed [10, 36]. Changes in the microcirculation and blood supply of tissues were prerequisites for myocardial ischemic hypoxia. Cardiomyocyte hypertrophy developed along with foci of necrosis and destruction of stromal elements, manifesting regenerative–plastic insufficiency of myocardial tissue.

Although the study did not evaluate the informative index of mitochondrial–myofibrillar ratio in cardiomyocytes [35], analysis of morphometric (cell nuclei) and bioenergetic indices of myocardial cells of experimental animals under various modes of vibration confirmed the association between the increase of morphohistological signs of cardiac degeneration and energy potential supply [10]. This indicates the direction of the vector of pharmacological effect on the correction of energy potential.

CONCLUSIONS

The ability of the tissue to maintain energy potential was significantly associated with stable structure, providing an ideal ratio between the spatial configuration of heart cavities and ability to effectively contract and overcome

pre- and post-load on the myocardium during different experimental modes of vibration (7, 21, and 56 sessions with a frequency of 8 and 44 Hz). Functional, morphological, and electrophysiological remodeling are components of a single pathological process and develop in parallel.

During remodeling, compensatory mechanisms, such as the gradual loss of myofibrils by cardiomyocytes, are activated. This reduces the myocardial demand for energy substrates. Additionally, the cell nucleus increases in size, allowing for an increase in contractile cell diameter.

Despite sufficient studies about changes in the morphological structure of myocardial tissue under vibration [39], up-to-date data on the characterization of changes in the system of synthesis and degradation of collagen filaments, order of collagen bonds between individual cardiomyocytes, state of the system of matrix metalloproteinases [40–42] involved in the process of vibration-mediated remodeling, level of contractile protein expression, and phenotype of cardiomyocytes with reexpression of fetal genes remain absent [16]. Further experimental and clinical studies are warranted for the actualization of directions and target points for pharmacological correction of cardiac structure and function disorders in HAVS [43, 44].

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