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Compensatory mechanisms in the course of the diastolic dysfunction development at stress cardiomyopathy

Aim	To study the activation sequence of compensatory mechanisms during the development of diastolic dysfunction.
Material and methods	The study was performed on rats with stress cardiomyopathy induced by high doses of isoproterenol (120 mg/kg twice a day). Heart function was studied 3-5 and 8-10 days after the injection by echocardiography and left ventricular (LV) catheterization. The content, isoform composition of the sarcomeric protein connectin (titin) and its mRNA content were also measured.
Results	The early period was characterized by the presence of systolic dysfunction evident as a decrease in the minute volume due to impaired myocardial and LV contractility, and slower LV filling and relaxation. Compensatory changes at this stage were manifested as increases in the left atrial volume and diastolic pause duration due to reduced contraction rate and arterial elasticity. The content of the more compliant N2BA connectin isoform and its mRNA was increased. These changes facilitated increases in LV filling and ejection. In the second period, diastolic dysfunction developed, when the minute volume, contraction rate and LV contractility became normal, although the left atrial pressure remained elevated, and the aortic diameter and LV wall thickness increased. The increased content of the N2BA isoform remained, and this was associated with stable slowing of LV relaxation.
Conclusion	The study showed that in the initial period, compensation is achieved by urgent mobilization of the circulatory system, while the improvement in myocardial contractility is secondary.

Keywords	Diastolic dysfunction; isoproterenol; heart; contractile function; relaxation; connectin (titin)
For citations	Lakomkin V.L., Abramov A.A., Prosvirnin A.V., Mikhailova G.Z., Ulanova A.D., Gritsina Y.V. et al. The Compensatory Mechanisms in The Course of the Diastolic Dysfunction Development at Stress Cardiomyopathy. Kardiologiia. 2025;65(7):10–16. [Russian: Лакомкин В.Л., Абрамов А.А., Просвирнин А.В., Михайлова Г.З., Уланова А.Д., Грицына Ю.В. и др. Компенсаторные механизмы в динамике развития диастолической дисфункции при стрессорной кардиомиопатии. Кардиология. 2025;65(7):10–16].

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Introduction

Diastolic dysfunction (DD) occurs as a result of myocardial damage caused by various causes, common to which is an impairment of contractility. One of these pathologies is stress – induced cardiomyopathy, also known as takotsubo cardiomyopathy, which occurs due to the excessive action of catecholamines on the heart. It is manifested by acute left ventricular (LV) dysfunction and ballooning of its apex [1, 2]. An adequate model for studying this pathology is the effect of the synthetic beta-adrenergic agonist isoproterenol [2, 3]. The dosages and methods of administration used are very different – continuous administration through an osmotic pump [4, 5], single or double administration [6–9], the use of several doses during the week [10–12].

It is known that in the initial period of action of a cardiotoxic dose of isoproterenol, small-focal ischemic lesions occur in the myocardium [8, 13], especially in the region of the LV apex, which contains the largest number of beta-adrenergic receptors [2]. This is manifested by ballooning of the tip [1], a decrease in stroke volume, an increase in the heart rate, a decrease in blood pressure (BP), a slowdown in relaxation and a decrease in LV filling [14]. However, the ejection fraction (EF) remained the same, which indicates the development of DD. These changes are similar to those

ISSN 0022-9040. Kardiologiia. 2025;65(7). DOI: 10.18087/cardio.2025.7.n2880

that develop in moderate myocardial infarction [11, 15]. But the compensatory changes that occur after 1–2 weeks are of the same type – hypertrophy and dilation of the heart develop, and these changes are proportional to the initial dose of isoproterenol [2, 13], fibrosis [10], systolic dysfunction disappears, but DD increases [9], the E/A ratio decreases [4, 5, 16], and diastolic elasticity the myocardium increases [10]. However, the sequence of inclusion of various compensatory factors was not the subject of the study, and it seems necessary to understand the nature of the considered form of chronic heart failure. In this work, we tried to fill this gap by studying the state of the heart and circulatory system in the process of impaired myocardial contractility, which underlies DD, as well as by investigating changes in the isoform composition of connectin, a giant sarcomeric protein that determines the viscoelastic properties of the heart. For this purpose, we investigated the pumping function of the heart 3–5 and 8–10 days after a double injection of isoproterenol.

The aim

Study of the sequence of activation of compensatory mechanisms in the formation of diastolic dysfunction.

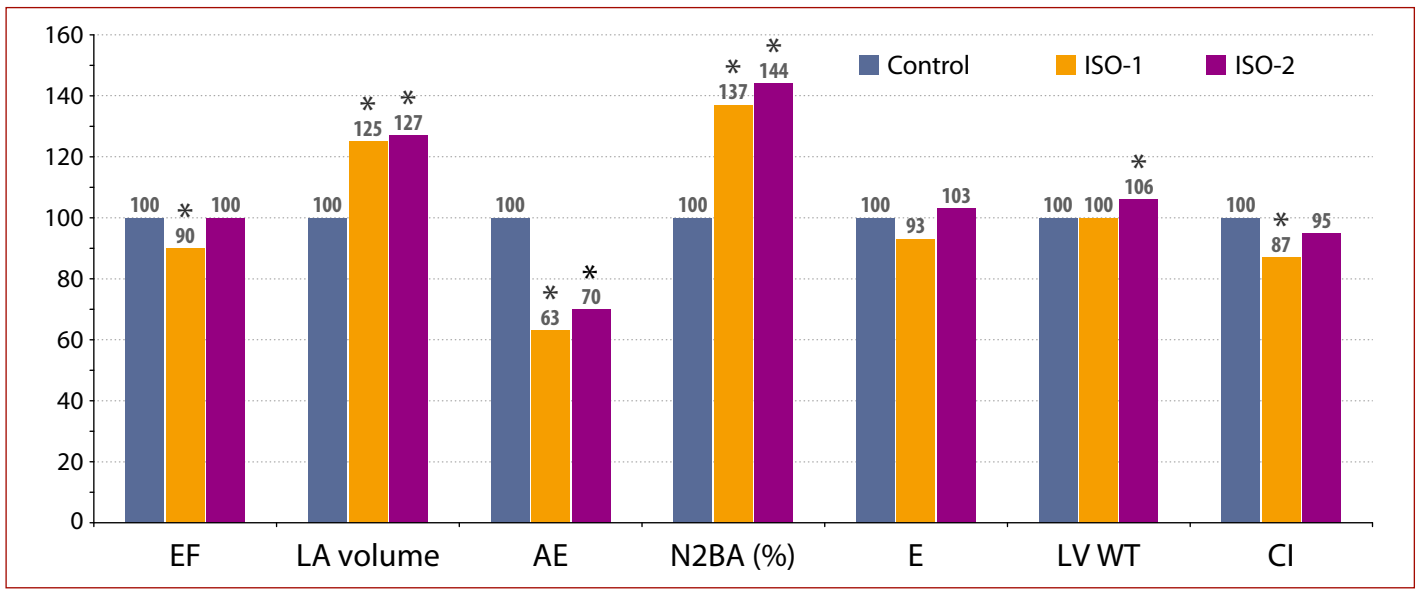
Material and methods

Male Wistar stock rats weighing 350–400 g and aged 5–6 months were used in the work. The animals were kept in the bio clinic of the cardiocenter in cages of 5 animals with free access to dry food and water. The light regime was controlled (12 hours of illumination, 12 hours of dimming) with a sufficient change in air volume and a temperature of 19–23 °C.

The study was conducted in accordance with the basic rules set out in the fundamental documents governing the conduct of experiments on laboratory animals and the conditions of their detention (Helsinki Declaration, 2000, Rules for conducting high-quality clinical trials in the Russian Federation (approved by the Ministry of Health of the Russian Federation on December 29, 1998). OST 42-511-99, Order of the Ministry of Health of the USSR No. 755 dated August 12, 1977 "On measures to further improve the forms of work using experimental animals"). The study protocol was approved by the Bioethics Commission of the Federal State Budgetary Institution "NMIC of Cardiology named after Academician E. I. Chazov" Ministry of Health of the Russian Federation (protocol of meeting No. 2 dated 03/20/2023).

The study used 36 rats, which were all initially examined using transthoracic echocardiography (EchoCG) under anesthesia with zolethyl-100 (5 mg/kg), as described previously [17]. After this, the animals were randomly divided into three groups of 12 rats each: one group served as a control, and the other two groups received two subcutaneous injections of isoproterenol at a dose of 120 mg/kg each, with a break of one day between injections [8], so that the cumulative dose was 240 mg/kg. The experiments were conducted 3–5 days and 8–10 days after the last injection. In addition, LV catheterization was performed under Zolethyl-100 anesthesia (5 mg/kg) using a standard FTH-1912B-8018

Central illustration. Relative changes in indicators after 3–5 (ISO-1) and 8–10 days (ISO-2) of isoproterenol administration at a dose of 240 mg/kg



EF, ejection fraction; LA, left atrium; AE, arterial elasticity; N2BA, titin isoform; E, LV filling velocity; WT, wall thickness; CI, contractility index.
*p<0.05, significantly different from the control group.

catheter inserted through the right carotid artery and an ADV500 amplifier (Transonic, Canada). LabChart Ad Instruments 8.1.2 software (Australia) was used to calculate more than 20 contractile function parameters during the cardiac cycle [17]. In addition, detailed analysis of the relaxation phase was conducted in each experiment [18].

After the completion of the acute experiment, all hearts were frozen in liquid nitrogen, followed by the determination of the content and isoform composition of connectin (titin), as well as the mRNA content of this protein. Electrophoretic separation of connectin isoforms, including the NT isoform found in mammalian striated muscles [19], was performed in a 2.1–2.3% polyacrylamide gel reinforced with agarose, obtained by the method [20]. The connectin content was evaluated in relation to the content of myosin heavy chains.

The expression of connectin (titin) mRNA in the myocardium was measured using real-time polymerase chain reaction (PCR). Total RNA was extracted from 100 mg of frozen tissue using the ExtractRNA kit (Eurogen, Russia), following the manufacturer's instructions. The RNA concentration was measured using a NanoDrop 1000 spectrophotometer (Thermo Scientific, USA). Reverse transcription was performed using M–MLV reverse transcriptase (Eurogen, Russia). The resulting cDNA was used for real – time PCR with primers specific for the genes of protein isoforms of the connectin: for the N2B isoform: F CCAACGAGTATGGCAGTGTCA, R TGGGTTCAGGCAGTAATTGC; for the N2BA isoform: F CGGCAGAGCTCAGAATCGA, R GTCAAAGGACACTCACACTCAAAA. The glyceraldehyde-3-phosphate dehydrogenase GAPDH gene was used as a reference gene: F GCAAGAGAGAGGCCCTCAG, R TGTGAGGGAGATGCTCAGTG.

Statistical processing of the obtained data was performed in the R software environment (4.2.2) using the «emmeans» package (1.10.2) after a preliminary check of the data for the normality of the distribution. The data is presented as M±SEM (average ± error of the average). The comparison results were obtained by using analysis of variance (ANOVA), followed by posterior Student's t-tests. The p-value for multiple comparisons was calculated using the Scheffé method, which is implemented in the "multcomp" package (version 1.4–25). The results were considered statistically significant if the p-value was less than 0.05.

Results

Contractile function of the heart

The first study period (3–5 days) was characterized by significant changes in the properties of the myocardium, mainly its contractility. According to EchoCG data, the EF was reduced by 12%, and the shortening fraction by 23% (Table 1).

Table 1 shows the results of EchoCG of all rats, which were further divided into 3 groups of 12 animals for ventriculography (acute experiment). The data of these groups are presented in the table. 2 with the exception of three unsuccessful experiments.

Table 1. Echocardiographic examination of the hearts of rats treated with isoproterenol (ISO) after 3-5 and 8-10 days

Indicator	Control (n=36)	ISO 3–5 days (n=12)	ISO 8–10 days (n=12)
Number of rats	36	12	12
EDV, μl	362±10	377±15	371±25
EF, %	72,1±1,36	65,2±2,58*	72,9±2,35#
ShF, %	18,6±0,82	12,1±1,41***	14,7±1,41*
DIR, ms	13,4±0,49	17,4±0,85***	19,8±0,85***
TAW LV, mm	1,20±0,02	1,3±0,09	1,23±0,03
TPW LV, mm	1,14±0,02	1,13±0,03	1,21±0,03*#
Volume of the left atrium, μl	103±4,46	129±7,72*	131±7,72**
Diameter of the aorta, mm	3,36±0,05	3,42±0,08	3,59±0,08**
E, mcl/s	70,4±1,66	65±2,88	71,9±2,88
E/A	3,42±0,13	3,16±0,2	3,17±0,18

* – p<0,05; ** – p<0,01; *** – p<0,001 compared to the control, # – p<0,05 compared with ISO 3–5 days; EDV – End diastolic volume of the left ventricle; DIR – duration of isovolumic relaxation; TAW LV – thickness of the anterior wall of the left ventricle, TPW LV – thickness of the posterior wall of the left ventricle; E – fast filling speed LV. E/A – the ratio of fast and slow filling speeds LV, EF – Ejection fraction, ShF – The shortening fraction

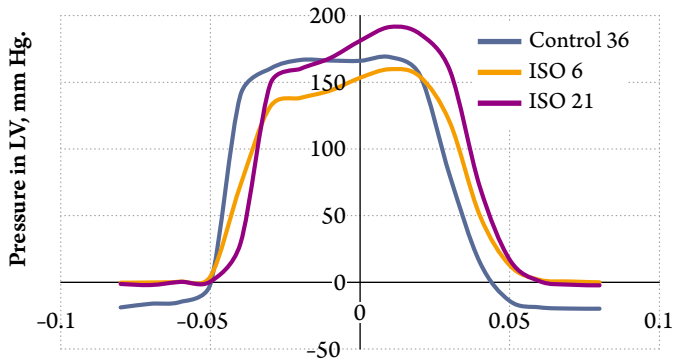
Table 2. Hemodynamics at two periods after administration of isoproterenol (ISO)

Indicator	Control (n=10)	ISO 3–5 days (n=11)	ISO 8–10 days (n=12)
Number of rats	10	11	12
Heart rate, beats/min	391±9.21	352±8.78**	397±8.41##
Cardiac output, ml/min	76.6±5.8	59.5±5.24	67.1±5.02
Systolic pressure in LV, mm Hg	181±6.59	158±5.96*	180±5.71#
Maximal Rate of development pressure, mm Hg/s	18667±790	15304±714**	17264±684#
Contraction Index, s^{-1}	182±6,92	158±6,26*	173±6
Time to pick, ms	46±3	54±2*	48±1#
Minimal pressure in LV, mm Hg	–2,4±0.87	0,59±0,87*	–2,02±0.75#
Arterial stiffness Ea, mm Hg/ml	1.53±0.14	0.96±0.1*	1.08±0.09*

* – p<0,05; ** – p<0,01 compared to the control; # – p<0,05; ## – p<0,01 – compared to ISO data 3–5 days, LV— the left ventricle .

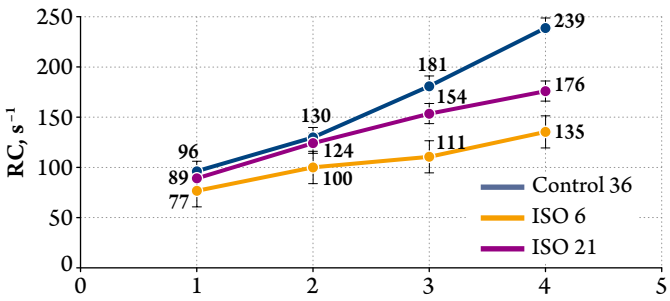
ISSN 0022-9040. Kardiologiia. 2025;65(7). DOI: 10.18087/cardio.2025.7.n2880

Figure 1. Typical dynamics of pressure in the left ventricle in the cardiac cycle



The numbers indicate the order of the experiments. ISO 6 was conducted after 3-5 days, and ISO 21 was conducted after 8-10 days.

Figure 2. Dynamics of the growth of the relaxation constant (RC) of the left ventricle from the initial, isovolumic (1) to the final, auxovolumic (4) in the control groups, 3-5 and 8-10 days after the administration of isoproterenol (ISO)



Analysis of ventriculograms revealed that the left ventricular systolic pressure was decreased by 13%, and the time to reach peak pressure was increased by 17%. The maximum rate of left ventricular pressure development was decreased by 18%, while the contractility index was reduced by 13%. The pumping function was also affected, with the cardiac output decreasing by 23%, mainly due to a reduction in stroke volume of 15%. (Table.2).

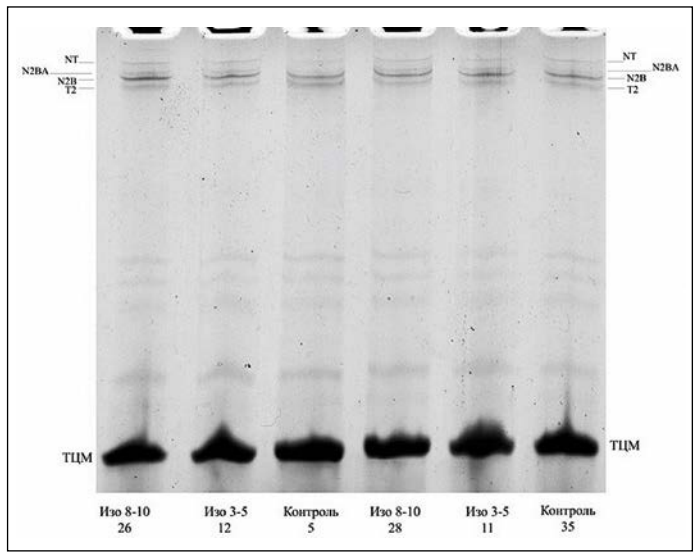
At the second stage of the study (8–10 days) all indicators of contractile function approached the control ones. LV shortening fraction, LV systolic pressure, maximum rate of pressure development, contractility index, frequency of contractions, and minute volume did not differ from the control, and EF became normal (Table 1 and 2). Delayed relaxation remained, but the final diastolic pressure decreased significantly compared to that in the first series of experiments (Table 2). The volume of the left atrium increased, but the thickness of the posterior wall of the left ventricle (LV) and the diameter of the aorta also increased (Table 1). Additionally, the shape of the pressure curve in the LV normalized (Figure 1) – in the first set of experiments, a slowdown in the rise and fall of pressure in the left ventricle was clearly visible, whereas in the second set of experiments these values were identical to those in the control group.

A detailed analysis of the LV relaxation dynamics showed a steady increase in the isovolumetric relaxation constant in all experiments. However, in the experiments of the first period, this increase significantly lagged behind the control curve (Fig. 2). The auxovolumetric constant value in the first series of isoproterenol administration was reduced by 44% ($p < 0.001$) and in the later series by 26% ($p<0.02$). These findings indicate a slowing down of the final relaxation interval in both groups with the administration of isoproterenol, whether it was short-term (3–5 days) or longer-term (8–10 days).

Investigation of the content, isoform composition of connectin (titin) and its mRNA content

The ratio of the sum of intact isoforms of connectin N2B+N2BA+ NT and the content of heavy chains of myosin in the first period of action of isoproterenol decreased to 91±12% ($p<0.05$) compared with the control, mainly due to a decrease in the content of the NT isoform (81±18%; $p<0.01$). During the second period of action of isoproterenol, these changes returned to normal. The content of the N2BA isoform (as a percentage of the N2B content) in the first term increased from 16±3% in the control to 22±3% ($p<0.01$) and to 23±3% ($p<0.01$) in the second term, i.e. the content of the N2BA isoform was steadily increased (Fig. 3). The ratio of the content of proteolytic T2 fragments of connectin to the total content of intact (full-size) isoforms of this protein did not change (Fig. 3).

Figure 3. Changes in the isoform composition of connectin/titin in the myocardium of rats under the influence of isoproterenol



Bands of isoforms NT, N2BA, N2B, proteolytic fragments of titin (T2), and heavy chains of myosin (MHC) are indicated.

According to the results of PCR analysis, during the first period of action of isoproterenol, an increase in the content of N2B mRNAs (2.1±1.5 times; p<0.01) and N2BA (2.4±2.1 times; p<0.01) of connectin isoforms was observed. In the second term, both indicators returned to normal.

Discussion

To understand the nature of compensatory changes, it is very important to know why myocardial contractility decreases under the influence of isoproterenol. An ex vivo study revealed that the ratio between the basal mechanical efficiency index (BME) and oxygen consumption (MVO2) decreases with an increase in metabolic demand during beta-adrenergic stimulation, which indicates the separation of BME and mitochondrial energy production [9].

The study of mitochondria revealed a decrease in oxidative metabolism, fragility of membranes and the presence of increased oxidative stress. The form of calcium signals in cardiomyocytes was distorted, although the expression of Ca^{2+}-ATPase of the sarcoplasmic reticulum SERCA, RyR2 gate protein, or phospholamban remained unchanged. Thus, the decrease in cardiac contractility is based on insufficient production of ATP, which is necessary for myofilaments and Ca^{2+} transport using SERCA, while exacerbation of oxidative stress can enhance the diastolic activity of RyR2, disrupting the cyclical excitation [9]. Consequently, cardiomyocytes are forced to function at a reduced level of myofibril activation. This view is supported by the results of work using one of the derivatives of nitric oxide HNO. Its administration promoted the absorption of Ca^{2+} by the structures of the sarcoplasmic reticulum and accelerated relaxation of isolated cardiomyocytes, as well as LV in rats with DD, which occurred after 4 weeks of isoproterenol administration [21].

In our experiments, during the first period of action of isoproterenol (3–5 days), reduced contractility was manifested by a decrease in LVEF and LV shortening, a decrease in the maximum rate of LV pressure and contractility index, and a decrease in stroke volume. Under these conditions, the circulatory system tends to increase blood flow to the LV and reduce ejection resistance. In full accordance with this, the volume of the left atrium increased, the frequency of contractions slowed down, prolonging the diastolic pause, and the elasticity of the arterial wall decreased. However, these compensatory changes were insufficient, and the minute volume was reduced. In the next phase, other mechanisms were connected.

Although the shortening fraction and volume of the left atrium remained the same, thickening of the posterior LV wall was observed, indicating incipient myocardial hypertrophy, and dilation of the aorta, which facilitated LV ejection, as well as minimal LV pressure and arterial wall elasticity. As a result, the maximum rate of LV pressure development, contractility index, stroke volume, frequency of contractions and minute volume were restored.

The state of LV relaxation is an important factor in determining the degree of DD. During the initial period of isoproterenol administration, the isovolumic relaxation time of the LV increased by 1.5 times compared to the control group (Table 1). The initial isovolumic relaxation constant decreased by 24% and the final auxiliary relaxation constant decreased twofold (Fig. 2). The study in the second term showed a definite improvement in left ventricular relaxation. The initial isovolumic relaxation constant was not different from the control group, but the final auxvolumic constant was about 40% lower. This indicates the preservation of diastolic dysfunction. We have recently seen similar changes in patients with diastolic dysfunction on the background of coronary artery disease [22].

The increase in the relaxation constant as the pressure in the left ventricle decreases is explained by the gradual activation of the passive relaxation component. This component ensures a gradual restoration of the initial sarcomere length, a role played by the sarcomeric protein connectin. Connectin was discovered in 1976 [23] and is better known as titin. Its spring-like structure contracts during sarcomere contraction and returns to its original position upon relaxation, pulling the ends of the myosin filaments back to their original positions [24, 25]. The more stiffer N2B isoform is responsible for this function, while the more compliant N2BA isoform provides less resistance to the stretching of myocardial fibers during diastole. The higher the spring elasticity, the faster the original (before reduction) length of the sarcomeres is restored. Our data suggest that the spring elasticity provided by the N2B isoform decreases sharply during the initial period of isoproterenol action. This was combined with an increase in the proportion of the more compliant N2BA isoform, which is consistent with the literature data [26, 27]. As a result, the stiffness of the myocardium in the diastole phase decreases, thereby facilitating LV filling.

Conclusion

The results of our study show that at an early stage of experimental myopathy (ISO 3–5) in the presence of systolic dysfunction, partial compensation of cardiac output is achieved through urgent mobilization of the circulatory system aimed at increasing blood flow to the left ventricle and reducing ejection resistance. In

ISSN 0022-9040. Kardiologiia. 2025;65(7). DOI: 10.18087/cardio.2025.7.n2880

the same vein, there is information about the predominant expression and an increase in the proportion of the more compliant isoform of N2BA connectin. This change persisted at a later stage of experimental cardiomyopathy. However, incipient myocardial hypertrophy and improved relaxation contributed to a decrease in the minimum diastolic pressure in the left ventricle and an increase in myocardial contractile function, leading to diastolic dysfunction.

The authors' contribution to the work

Kapelko V.I., V.L. Lakomkin, and I.M. Vikhlyantsev. – the idea of the work and the design of experiments; A.A. Abramov and A.V. Prosvirnin – performing catheterization and echocardiography of the left ventricle, digitization and data processing; G.Z. Mikhailova, A.D. Ulanova – determination of connectin content and isoform composition; Yu.V. Gritsyna – determination of connectin mRNA content. V.L. Lakomkin, V.I. Kapelko and I.M. Vikhlyantsev – preparation and editing of the manuscript.

Funding

The work was carried out with the financial support of the Russian Science Foundation (grant No. 23-15-00275).

Conflict of interests

All authors declare that there is no potential conflict of interest that requires disclosure in this article..

The article was received on 20/01/2025

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ISSN 0022-9040. Kardiologiia. 2025;65(7). DOI: 10.18087/cardio.2025.7.n2880