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MARKERS OF STRUCTURAL AND FUNCTIONAL MYOCARDIAL REMODELING AND DETECTING THE EFFICIENCY OF TREATMENT OF ENDOTHELIAL DYSFUNCTION

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✓ ***Resume***

Cardiovascular disease is currently the most common cause of death in adults. Therefore, reliable and effective markers, in order to monitor coronary heart disease, as well as for therapeutic control, is one of the highest priorities in medicine. The aim of our study is to use echocardiographic markers to identify echocardiographic characteristics of patients with myocardial infarction and to correlate with the clinical picture, as well as to monitor the therapeutic effect of trimetazidine.

Keywords: Cadiomyocytes, coronary heart disease, myocardial infarction, echocardiography, trimetazidine.

MIOKARDNI TUZILISH VA FUNKSIONAL REMODELLANISH MARKERLARI VA ENDOTELIAL DISFUNKSIYASINI DAVOLASH SAMARALILIGINI ANIQLASH

Toshev B.B.

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✓ ***Rezyume***

Yurak-qon tomir kasalliklari hozirda kattalardagi o'limning eng keng tarqalgan sababidir. Shuning uchun ishonchli va samarali markerlar koroner yurak kasalligini kuzatish, shuningdek terapevtik nazorat uchun tibbiyotning eng ustuvor yo'nalishlaridan biridir. Tadqiqotimizning maqsadi miyokard infarkti bilan og'rigan bemorlarning ekokardiyografik xususiyatlarini aniqlash va klinik ko'rinish bilan o'zaro bog'liqlik, shuningdek trimetazidinning terapevtik ta'sirini kuzatish uchun ekokardiyografik markerlardan foydalanish.

Kalit so'zlar: kadiomiyotsitlar, koroner yurak kasalligi, miokard infarkti, ekokardiyografiya, trimetazidin.

МАРКЕРЫ СТРУКТУРНО-ФУНКЦИОНАЛЬНОГО РЕМОДЕЛИРОВАНИЯ МИОКАРДА И ВЫЯВЛЕНИЕ ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ

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✓ ***Резюме***

Сердечно-сосудистые заболевания в настоящее время являются наиболее распространенной причиной смерти у взрослых. Поэтому поиск надежных и эффективных маркеров для мониторинга ишемической болезни сердца, а также для терапевтического контроля является одним из важнейших приоритетов в медицине. Целью нашего исследования является использование эхокардиографических маркеров для выявления эхокардиографических характеристик пациентов с инфарктом миокарда и их корреляции с клинической картиной, а также для мониторинга терапевтического эффекта триметазидина.

Ключевые слова: кадиомиоциты, ишемическая болезнь сердца, инфаркт миокарда, эхокардиография, триметазидин.

Relevance

Cardiomyocytes (CM) are a special, cardiac, form of striated muscle cells. These are muscle cells that have the ability to spontaneously depolarize, which ensures their autorhythmic properties, as well as the ability to coordinate actions with other CMs, the effects of this property are tight junctions [1]. These features of the CM allow the heart to function as a pump [2, 3]. The regulation of CM activity is carried out through selective transport and binding of signal and effector molecules by the CM membrane and sarcolemma, in particular [4, 5], which guarantees contraction and relaxation of contractile fibers. The BM cytoskeleton forms a structural link between the extracellular environment and the contractile apparatus, allows you to change the BM geometry and their functional activity due to phosphorylation of cytoskeletal proteins. Fibrous structures consisting of myosin and actin are effectors of the contractile function of the CM. CMs contain a large number of mitochondria, which provide ATP energy for CM contraction and relaxation [6, 7].

The most common CVDs are coronary heart disease (CHD) and atherosclerosis [8]. CVD is associated with reduced quality of life and significant negative psychological, social and economic impacts.

IHD is the most common cause of death in the world [9]. WHO reports 740 million deaths per year worldwide, which is 13.2% (Organization Wh . World Health Organization report. May 2014, http :// www . who . int / mediacentre / factsheets / fs 310/ zh /). Myocardial infarction (MI) is the main manifestation of coronary artery disease, manifested by necrosis or apoptosis of the myocardium, causally associated with vascular occlusion of the coronary bed [19] and leading to the development of heart failure with a negative prognosis [20]. MI is the main cause of death in patients with coronary artery disease [13].

Ischemic heart disease is a pathophysiological condition caused by a mismatch between myocardial oxygen demand and its supply. Myocardial nutrition depends on the oxygen capacity of the blood and the volume of coronary blood flow. Ischemia is caused by myocardial oxygen demand at the time of occurrence of coronary artery spasm or intravascular coagulation at the site of atherosclerotic plaque rupture [10].

Ischemia leads to a sudden cessation of oxidative phosphorylation; thus, ischemic cardiomyocytes use alternative pathways for the formation of ATP. Since the reserves of high-energy phosphates in the form of creatine phosphate are rapidly depleted [11], anaerobic glycolysis becomes the main source of newly generated ATP and leads to a rapid accumulation of lactate in the ischemic myocardium. In the absence of perfusion, glucose cannot be delivered to cardiomyocytes; thus, the main substrate for glycolysis in the ischemic heart comes from intracellular glycogen stores. Even at the highest rate, anaerobic glycosis cannot replace the much more efficient ATP-producing capacity of oxidative phosphorylation; as a result, ATP is consumed much faster than it is produced. Intracellular acidosis progressively develops due to the accumulation of lactate and inhibits many enzymes of the glycolytic pathway; thus, after 15-20 minutes of ischemia, the rate of anaerobic glycolysis decreases markedly. Glycolysis eventually stops, despite the presence of glycogen stores in cardiomyocytes. Obviously, ischemia has a profound effect on the content of adenine nucleotides in the myocardium. ATP is consumed much faster than it is produced, and the concentration of ADP rises. Adenylate kinase converts ADP to ATP and AMP; ATP is used and AMP is converted to adenosine by 5'-nucleotidase. Adenosine diffuses into the interstitium, where it is converted to inosine and hypoxanthine. A pronounced decrease in the level of ATP in the ischemic myocardium is associated with the development of irreversible changes in cardiomyocytes, since cells depleted of energy reserves cannot maintain homeostasis [12, 13].

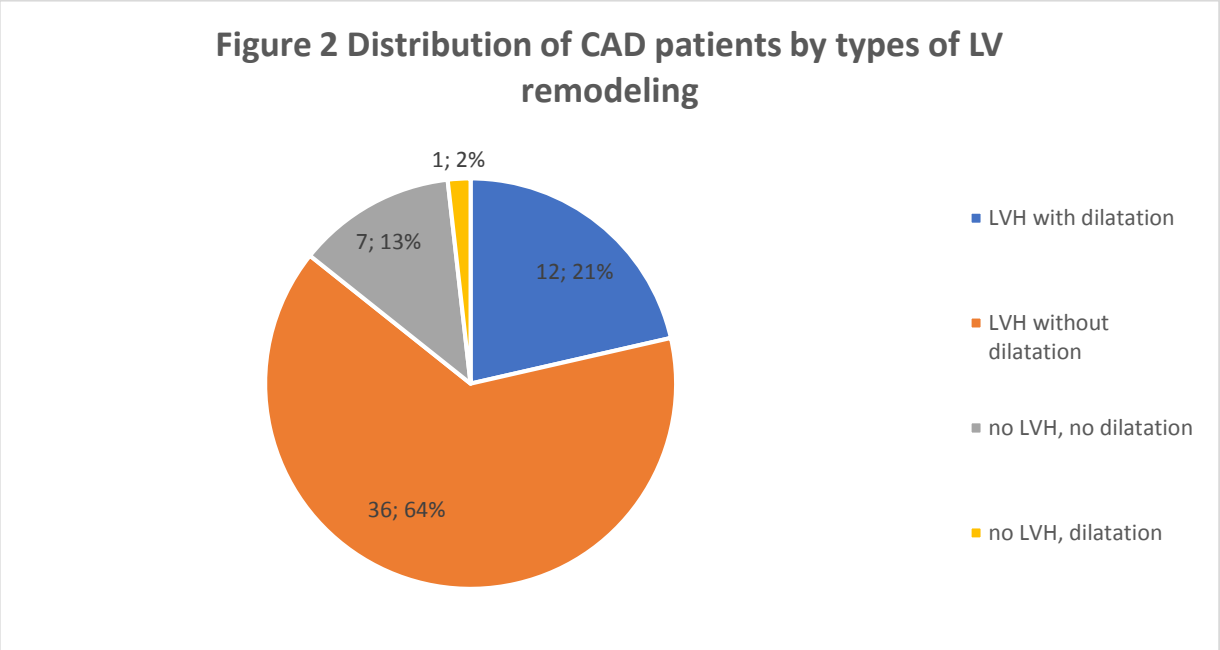
Descriptive studies suggest that both apoptosis and necrosis are involved in cardiomyocyte death after myocardial ischemia. Ultrastructural studies documenting cell swelling and membrane disruption in a large number of infarcted cardiomyocytes, as well as an intense MI-induced inflammatory response, suggest an abundance of necrotic cardiomyocytes. On the other hand, a large number of apoptotic cardiomyocytes have been identified in infarcted hearts using both ultrastructural and histochemical approaches [14, 15]. The relative contribution of apoptosis and necrosis to the death of infarcted cardiomyocytes remains poorly understood. Major limitations in the experimental methods used to identify apoptotic and necrotic cells make the rigorous quantification of apoptotic and necrotic cardiomyocytes in the infarct area a particularly challenging task. It has been suggested that during ischemia, most cardiomyocytes may undergo necrosis, while reperfusion may activate powerful proapoptotic pathways, leading to a marked increase in apoptotic death of cardiomyocytes [13, 16, 17]. Most cardiomyocytes in the infarction zone die within the first 24 hours after coronary occlusion. At a later date, activation of pro-inflammatory pathways in the infarction zone and biomechanical stress can cause a second wave of cardiomyocyte death, which is much less intense than acute ischemic loss of cardiomyocytes. Although in experimental models individual cardiomyocytes may undergo apoptosis in viable remodeling

segments weeks or months after acute infarction, the contribution of this process to the progression of ventricular dysfunction is unknown [13, 18].

Materials and methods

The study included 56 patients with coronary artery disease who are under outpatient observation at the RSNPCT and MR named after N.A. Semashko MH RUz. The diagnosis was based on the clinical picture - clinical signs of angina pectoris II - III functional classes, myocardial infarction (MI) in history or electrocardiographic signs. Verification of the diagnosis was based on coronary angiography and coronary revascularization.

When collecting an anamnesis of patients, we made sure that 32.1% (n=18) of patients had a lesion of only one vessel; 35.7% (n=20) of patients had vascular lesions in two and 33.9% (n=19) of patients had vascular lesions in three coronary arteries (Figure 1).



1-Figure. Distribution of IHD patients included in the study, depending on the number of affected pools.

The average age of the patients was 55.94±1.29 years, height - 170.24±1.12 cm, weight - 77.72±1.79 kg. As a control group (CG), the study included 20 healthy volunteers without signs of damage to the cardiovascular system, of comparable age and anthropometric characteristics.

All patients included in the study received basic therapy for coronary artery disease (Table 1).

Table 1

Basic therapy for IHD and CHF in patients included in the study

Drugs	Number of patients	Relative share (%)
Beta-blockers	102	94.44%
ACE inhibitor	32	29.63%
ARB	76	70.37%
Sacubitril	51	47.22%
BKK	28	25.93%
Antiplatelet agents	92	85.19%
Anticoagulants	22	20.37%
Antiarrhythmics	31	28.70%
Statins	99	91.67%

Note ACE inhibitors - angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, slow calcium channel blockers.

After the initial examination of all patients included in the study, trimetazidine 80 mg, orally, once a day (Preductal OD 80) was additionally included in the treatment regimen. The observation period was 3 months, after which a control examination of the state of the myocardium was carried out. Thus, we calculated the effectiveness of trimetazidine in patients with coronary artery disease, depending on the results of echocardiography.

During the study, all patients and representatives of the main and control groups included in the study were examined, during which the structural and functional state of the myocardium was studied (echocardiography - EchoCG). In addition, patients of the main group were re-examined with echocardiography after treatment in order to analyze the effectiveness of trimetazidine in patients with chronic coronary artery disease.

EchoCG examination was carried out on an ultrasound scanner S 40 Exp. A convex sensor with a frequency of 2-7.5 MHz was used. The examination was carried out in the morning in the position of the patient on the left side and on the back, after a 10-minute rest. The examination included scanning using standard ultrasound windows and EchoCG positions. The study protocol included registration of the parameters of the structural and functional state of the heart and features of intracardiac blood flow (Table 2).

Table 2

Protocol for EchoCG examination of persons included in the study

Index	Designation	Position	Method of determination
Left atrial volume indexed to body surface area	iLP	A2S/A4S	Simpson method
Left ventricular volume indexed to body surface area	LVH	A2S/A4S	Simpson method
Ejection fraction of the left ventricle	EF LV	A2S/A4S	(LV end-diastolic volume - LV end-systolic volume)/ LV end-diastolic volume*100%
myocardial mass indexed to body surface area	LVMI	A2C	Sink method
Diastolic thickness of the interventricular septum	MZHP	PLAX	From the border of the RV endocardium to the border of the LV endocardium
Diastolic thickness of the posterior wall of the left ventricle	ZSLZH	PLAX	From the border of the endocardium to the border of the epicardium
Relative wall thickness of the left ventricle	UTS	PLAX	(diastolic thickness of the interventricular septum + diastolic thickness of the posterior wall of the left ventricle) / end diastolic diameter of the left ventricle
Sphericity index	IP	A4C	Short diameter of the left ventricular cavity at the end of diastole / long diameter of the left ventricular cavity at the end of diastole
Regional contractility disorder index	INRS	Parasternal and apical positions, all views	Arithmetic mean score of systolic thickening of all visualized segments (0 - hyperkinesis, 1 - normokinesis , 2 - hypokinesis, 3 - akinesis , 4 -

			dyskinesia)
Tei index for right and left ventricle	Tei PJ, Tei LV	Apical	The ratio of the total duration of periods of closed valves (phases of isometric tension and phases of isovolumic relaxation) to the duration of the period of expulsion of the corresponding chambers
Mean pressure in the pulmonary artery	SRR LA	Parasternal on the short axis of the left ventricle at the level of the aortic valve, dopplerography of the systolic ejection flow on the pulmonic valve	The ratio of the duration of the acceleration of the flow of exile to the duration of the expulsion time, determination of the mean pressure in the pulmonary artery by nomograms
Right ventricular area indexed to body surface area	life expectancy	A4C	Planimetric measurement of pancreatic area
Prostate area reduction fraction	FUP PZH	A4C	(RV end-diastolic area - RV end-systolic area)/ RV end-diastolic area*100%
Right atrial area indexed to body surface area	IP	A4C	Planimetric measurement of the PP area
LV and RV diastolic function	DD	A4C, Doppler ultrasonography of diastolic flow through the tricuspid /mitral valve and tissue Doppler ultrasonography of the lateral edge of the satrioventricular rings	The ratio of the maximum rates of early and atrial filling and the rate of early filling of the ventricle and the rate of early diastolic displacement of the lateral edge of the atrioventricular ring

With statistical processing. All the results of the study were entered into the summary tables of the Excell editor Microsoft office. In the case of parametric values, the arithmetic mean value and its standard error were determined as a characteristic of the group. Intergroup comparison was carried out using Student's t-test for paired and unpaired values. Multiple comparisons were also made using Student's t-test adjusted for Bonferroni's correction for multiple comparisons. In the case of non-parametric values, the frequency of the trait in the group was estimated, the intergroup frequency difference was assessed using the tabular chi-square test and its reliability assessment according to the tables, taking into account the number of degrees of freedom. The dynamics of indicators against the background of ongoing activities was calculated as the ratio of the dynamics of the indicator to the initial value, expressed as a percentage. The dynamics in the group was defined as the arithmetic mean of the relative dynamics of all members of the group.

Results and discussions

R results before treatment. An echocardiographic study revealed that in patients with IHD, compared with CG, dilatation of all chambers of the heart was noted (Table 3): an increase in LA in patients with IHD compared with CG was 60%, LV - by 41.2%, RV - by 30% and PP - by 51.7% (significance of intergroup differences for all indicators - $p < 0.001$). The thickness of the IVS in patients with CAD was significantly greater (by 10.72%) compared with CG ($p < 0.01$), which reflects myocardial hypertrophy in response to ischemic apoptosis. The thickness of the PSLZH in the groups did not differ. The predominance of dilatation over hypertrophy led to a significant decrease in the OTC index in patients with coronary artery disease (by 1–6.3 %, the significance of intergroup differences was $p < 0.001$).

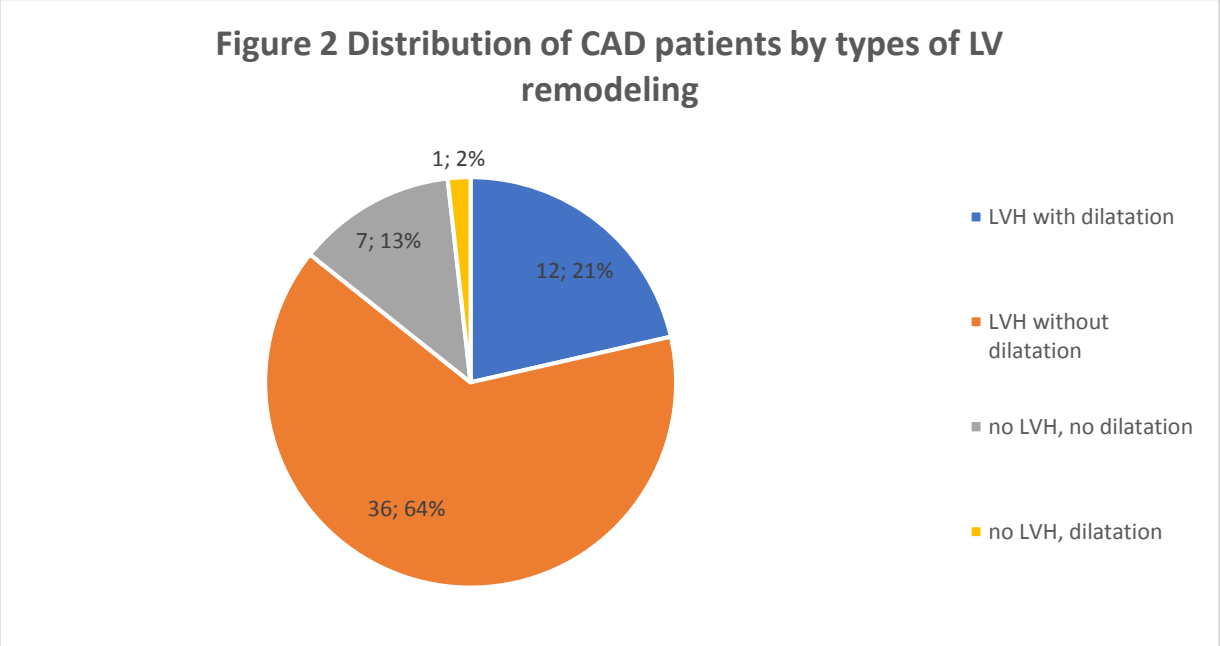
Note: * - significance of differences between groups. a - p < 0.05, b - p < 0.01, c - p < 0.001.

The mass of the LV myocardium in patients with coronary artery disease was increased by 95.3% compared with CG (p <0.001). Thus, in the group of patients with coronary artery disease, the majority of patients (48 people - 85.7%) had LV hypertrophy (LVH (left ventricular hypertrophy), LVMI (left ventricular myocardial mass index) of 110 g/m ^{2} or more) (Fig. 2).

Table 3

Comparative characteristics of the structural and functional state of the myocardium in patients with coronary heart disease and healthy individuals

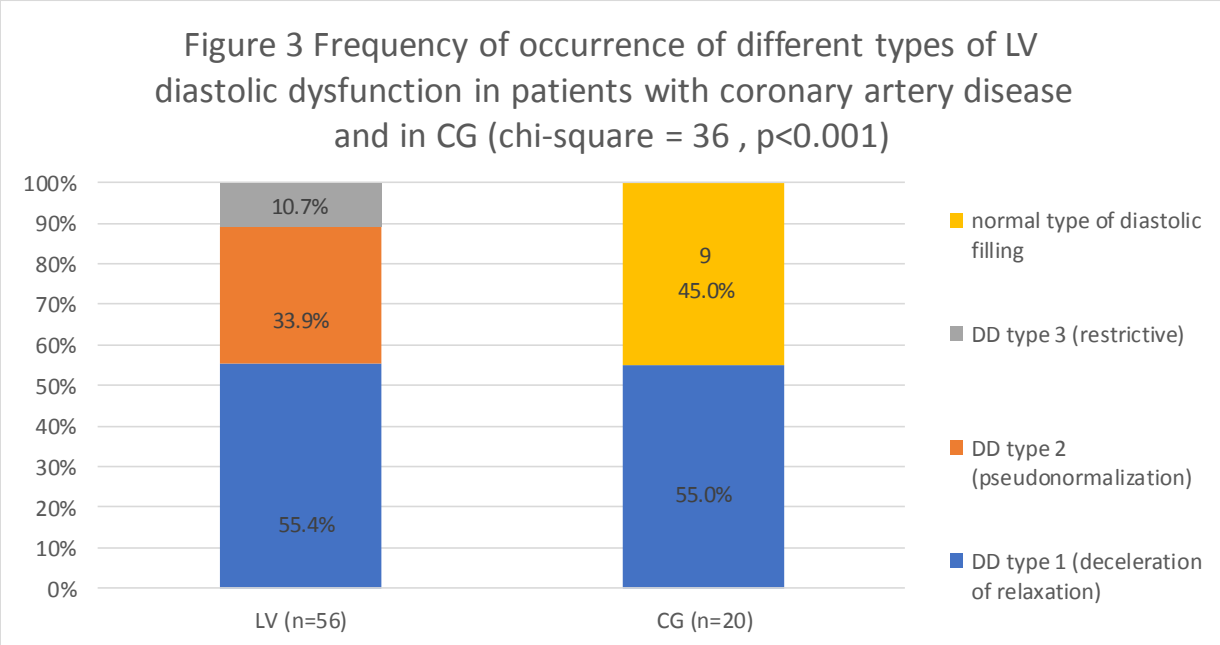
KG	CG (n=20)	all CAD (n=56)
iLP, ml/m2	26,90±1,75	43,04±1,25[c]
LV, ml/m2	51,55±1,55	72,80±3,43[c]
LV EF, % (simpson)	61,00±1,25	51,80±1,47[c]
LVMI, g/m2	87,20±2,52	170,34±7,04[c]
OTS, rel units	0,37±0,01	0,31±0,01[c]
MZHP, mm	9,40±0,23	10,45±0,27[b]
ZSLZh, mm	9,55±0,20	9,63±0,17
IP, rel units	0,54±0,07	0,65±0,01
INRS, score	1,00±0,00	1,55±0,06[c]
Tei LV, rel units	0,60±0,01	0,70±0,01[c]
avg LA, mm Hg	14,85±0,27	24,05±0,90[c]
Tei RV, rel units	0,63±0,01	0,69±0,01[c]
lifespan , cm2/m2	19,70±0,54	25,60±0,93[c]
FUP PZH, %	48,40±1,53	44,13±0,83[a]
IP , cm2/m2	15,25±1,12	23,14±1,91[c]



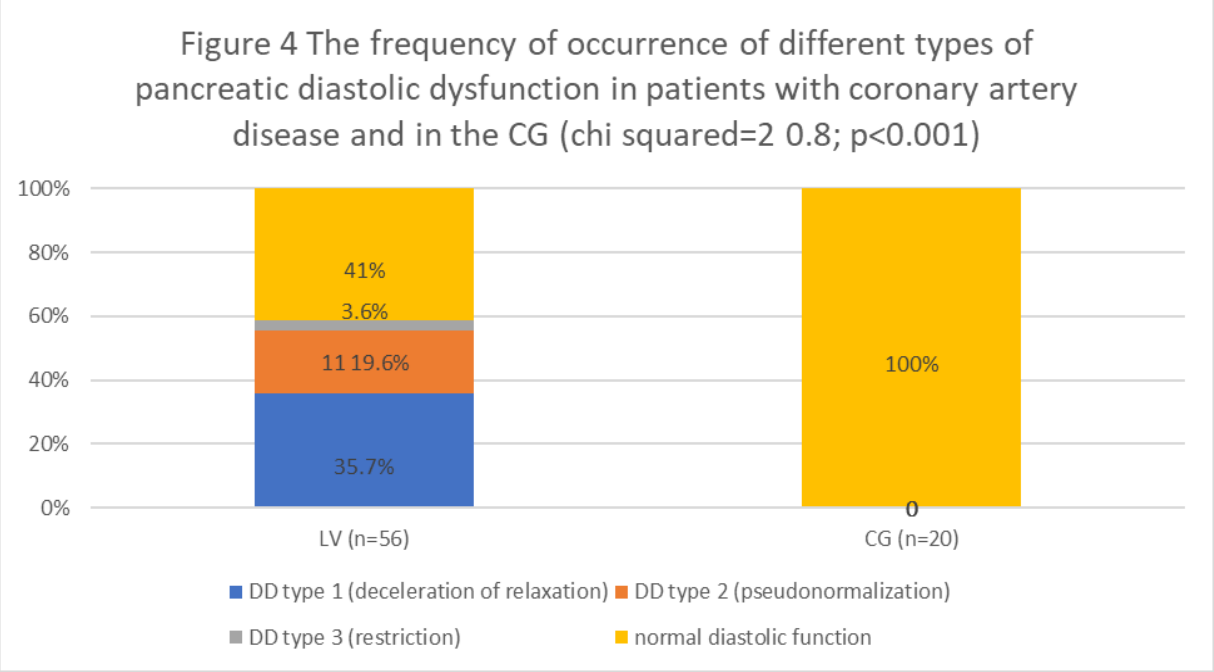
The systolic function of the left ventricle was characterized in patients with coronary artery disease and was characterized by an increase in INRS, which reflects regional contractility disorders, compared with CG (by 55%, p <0.001), as well as a decrease in the indicator of general systolic function - LV EF (-14.00% in relation to CG index, p <0.001) (Table 3).

The systolic function of the pancreas was characterized by a decrease in the PF index - an analogue of the EF for the pancreas, calculated by area due to the complex geometry of the pancreatic cavity. AF of the RV in patients with coronary artery disease was 8.8% less than in the CG ($p < 0.05$).

LV diastolic function revealed various variants of dysfunction in 100% of patients with coronary artery disease (Fig. 4), while in the CG diastolic dysfunction was observed only in 11 patients (significance of intergroup difference in the frequency of occurrence of various types of diastolic dysfunction between groups chi square = 36, $p < 0.001$). Among the disorders of diastolic function, the variant of delayed relaxation prevailed (Fig. 3).



Diastolic filling of the pancreas was also impaired in patients with coronary artery disease (59.26% of patients, Fig. 3.6), while in representatives of the CG diastolic filling was normal (significance of the intergroup difference in the frequency of occurrence of various types of diastolic filling chi square = 20.8, $p < 0.001$) (Figure 4).



Violation of LV diastolic and systolic function in patients with IHD led to an increase in the mean pressure in the LA system by 62 % (p <0.001), which indicates an increase in pressure in the LA cavity. In 41 patients of the IHD group (73 %), the average pressure in the LA, determined by the ratio of the acceleration time to the time of expulsion on the LA valve, exceeded the normal value (19 mm Hg) (Table 3) .

The study studied the indicator Tei - an integral index of myocardial functioning, characterizing the efficiency of myocardial work, that is, the time required for an effective change in intraventricular pressure. In patients with coronary artery disease, the Tei index was increased compared to the CG indicator (by 16.7 % for the left ventricle, p < 0.05 , and by 9.5 % for the right ventricle, nd) (Table 3).

The LA volume increased in patients with multivessel disease compared with patients with single vessel disease (p < 0.001 significant difference between patients with 2 and 3 vascular lesions versus patients with 1 vascular lesion). The LV volume, on the contrary, remained within normal limits in patients with 1 and 2 vascular lesions and significantly increased in patients with 3 against patients with 3-vascular lesions) (Table 4) .

The thickness of the IVS progressively decreases with an increase in the number of affected coronary beds (p < 0.05 - significant difference between groups with 1 versus 2 vascular lesions, p < 0.001 - significant difference between the group with 3 vascular lesions and other groups). At the same time, LVMI progressively increases (p < 0.01 - the significance of the difference between groups with 1 versus 2 vascular lesions, p <0.001 - the significance of the difference between the group with 3 vascular lesions and the rest of the groups), which is associated with progressive LV dilatation and the formation of ischemic cardiomyopathy, which is confirmed by a progressive decrease in the OTC indicator and an increase in IS (Table 4).

The areas of the right heart cavities progressively and significantly increased with the increase in coronary lesions (p < 0.001 significance of the difference in the areas of the right ventricles between all groups in terms of the number of affected vessels; p <0.001 significance of the difference in the area of the pancreas between patients with 3-vessel lesions and patients with 1 and 2 -x vascular lesion and p <0.05, the significance of the difference between patients with 1 vascular lesion versus 2 vascular) (Table 4) .

Left ventricular systolic function is characterized by a progressive increase in the regional contractility disorder index (p < 0.05 - significant difference between groups with 1 versus 2 vascular lesions, p < 0.001 - significant difference between the group with 3 vascular lesions and other groups) and a decrease LV EF (p <0.001 - significant difference between the group with 3-vessel disease and other groups). Accordingly, impaired LV pumping function is associated with a progressive increase in the mean pressure in the LA (p < 0.05 - significant difference between groups with 1 vs. other groups). The RV systolic function (RVF) progressively increased with an increase in the number of affected coronary basins (p < 0.001, the significance of the difference between groups with 3 and 1 vascular lesions, p < 0.05 , the significance of the difference between groups with 3 and 2 vascular damage), probably compensatory, to maintain the overall pumping function of the heart (Table 4) .

Table 4

The functional state of the myocardium in patients with coronary artery disease depending on the number of affected coronary pools

Sign	1	2	3
iLP, ml/m2	36,76±1,09	45,15±1,21[a]	45,94±1,69[a]
LV, ml/m2	57,27±1,53	60,20±1,34	96,49±3,76[ab]
LV EF, % (simpson)	58,12±2,04	53,38±0,93	46,09±1,24[ab]
LVMI, g/m2	129,33±4,09	152,83±5,94[a]	214,80±7,87[ab]
OTS, rel units	0,37±0,01	0,31±0,01[a]	0,26±0,01[ab]
MZHP, mm	11,79±0,32	10,73±0,25[a]	8,74±0,21[ab]
ZSLZh, mm	9,91±0,22	9,65±0,22	9,29±0,20
IP, rel units	0,58±0,04	0,65±0,01	0,70±0,01[ab]
INRS, score	1,27±0,04	1,49±0,06[a]	1,83±0,08[ab]
Tei LV, rel units	0,64±0,02	0,87±0,15	0,77±0,01[a]
avg LA, mm Hg	20,24±0,53	22,88±0,90[a]	30,00±1,29[ab]
Tei RV, rel units	0,63±0,02	0,85±0,15	0,75±0,01[a]
lifespan , cm2/m2	21,52±0,51	24,36±0,93[a]	31,83±1,31[ab]
FUP PZH, %	41,94±0,48	43,25±0,96	48,03±1,36[ab]
IP , cm2/m2	9,00±1,36	24,55±1,21[a]	33,66±1,89[ab]

Note: a - significance of differences with patients with 1 affected coronary basin - $p < 0.05$, b - significance of differences with patients with 2 affected coronary basins - $p < 0.05$.

R results after treatment. In terms of cardiac remodeling, in both groups there was a clinically insignificant decrease in the volume of the left chambers of the heart ($p < 0.01$, the significance of the difference with the initial data of iLP). A decrease in LV volumes against the background of a stable wall thickness led to a significant decrease in the OPV ($p < 0.001$ significance of the difference with the initial iLP data). A decrease in LV volume was associated with an improvement in the geometry of the cavity (reduction of SI, significance of differences from the initial data of LI). It was the change in the geometry of the left ventricle with a decrease in the degree of spherical deformity that led to a significant decrease in the TVR (by 35%) with a decrease in the left ventricle only by 2.19% ($p > 0.05$). Improvement in LV geometry contributed to an increase in the efficiency of LV myocardial functioning, which was manifested by a decrease in LV Tei ($p < 0.001$ significance of the difference from the initial data of iLL). These changes, despite the preservation of the initial LV EF and INRS, contributed to a decrease in the severity of postcapillary pulmonary hypertension (decrease in LA mean, $p < 0.001$, the significance of the difference with the initial iLP data). Decrease in pressure in the pulmonary circulation led to a decrease in the load on the pancreas, which was manifested by an improvement in the efficiency of myocardial function: a decrease in Tei of the pancreas and an increase in the RVF ($p < 0.001$ significance of the difference with the initial data iLP). All changes in cardiac structural and functional parameters were comparable in both comparison groups (Table 5).

Table 5

Comparative dynamics of myocardial and endothelial function parameters in patients with coronary artery disease against the background of including trimetazidine in standard therapy

	n =56		
P sign	Initially	3 months	Relative dynamics
iLP, ml/m2	43,04±1,25	42,50±1,22	-1,11±0,38
LV, ml/m2	72,80±3,43	70,20±2,69	-2,19±0,75
LV EF, % (simpson)	51,80±1,47	52,70±1,19	17,43±16,96
LVMI, g/m2	170,34±7,04	159,73±7,20	-3,33±3,67
OTS, rel units	0,31±0,01	0,42±0,01[a]	35,54±1,58
MZHP, mm	10,45±0,27	10,48±0,26	0,48±0,34
ZSLZh, mm	9,63±0,17	9,66±0,17	0,45±0,32
IP, rel units	0,65±0,01	0,57±0,01[a]	-11,91±0,48
INRS, score	1,55±0,06	1,55±0,06	0,00±0,00
Tei LV, rel units	0,70±0,01	0,46±0,01[a]	-34,39±1,20
avg LA, mm Hg	24,05±0,90	21,74±0,87[a]	-10,02±0,87
Tei RV, rel units	0,69±0,01	0,43±0,01[a]	-37,46±1,29
lifespan , cm2/m2	25,60±0,93	25,29±0,90	-0,93±0,67
FUP PZH, %	44,13±0,83	46,44±0,87[a]	5,33±0,45
IP , cm2/m2	23,14±1,91	22,98±1,91	-0,55±0,39

Note: a - significance of differences between groups - $p < 0.05$. Thus, the EchoCG study showed that in patients with coronary artery disease, compared with CG, there was a dilatation of all chambers of the heart, a violation of the structural and functional myocardium, correlating with each other. In addition, echocardiographic markers such as LVMI and VZHP indicated that patients with chronic CAD developed cardiac hypertrophy. It is well known that hypertrophy initially develops as an adaptive response to physiological and pathological stimuli, but pathological hypertrophy usually progresses to heart failure [21].

Cardiac hypertrophy becomes an inadequate decompensation when, in addition to cell growth and protein synthesis, the following processes occur: cell death, fibrosis, dysregulation of proteins

responsible for Ca2+ content, mitochondrial dysfunction, metabolic reprogramming, reactivation of fetal gene expression, impaired quality of proteins and mitochondria. The signaling mechanisms that induce these responses contribute to inappropriate remodeling and dysfunction of the heart and ultimately cause heart failure. Pathological conditions such as hypertension and myocardial infarction promote pathological hypertrophy mainly through neuroendocrine hormones and mechanical forces, accompanied by downstream signaling pathways distinct from those involved in physiological hypertrophy [21]. Although initially hypertrophy plays a compensatory-adaptive role against the background of tissue hypoxia and/or AH and MI, in the future it increases the likelihood of recurrent MI, as hypoxia of cardiomyocytes increases.

Ischemic myocardial remodeling is characterized by chamber dilatation, impaired diastolic filling of the ventricles, decreased myocardial contractility, and increased LA pressure.

In addition, we also found that, depending on the amount of coronary insufficiency, all echo markers (except markers of LVL, IS, Tei LV) of the structural and functional state of the heart progressively become more abnormal.

Trimetazidine is an anti-ischemic agent widely used in the treatment of coronary heart disease. It inhibits the long-chain mitochondrial enzyme thiolase 3-ketoacyl coenzyme A in mitochondria, resulting in improved mitochondrial metabolism by inhibiting myocardial uptake and oxidation of fatty acids and subsequent stimulation of glucose oxidation. FFA oxidation provides more energy, but is associated with increased oxygen consumption. With a lack of oxygen, the oxidative processes of FFA and glucose are disturbed, which paradoxically leads to an increase in the rate of FFA β-oxidation associated with even greater oxygen consumption, and glucose metabolism decreases, which leads to accumulation of lactate and, in extreme cases, the development of metabolic acidosis [22 , 23].

Unlike conventional drugs, trimetazidine does not affect coronary blood flow, contractility, blood pressure, or heart rate. It does not have significant negative inotropic or vasodilating properties at rest or during exercise; therefore, it can be perfectly combined with traditional CAD pharmacotherapy [22].

In our case, after additional treatment with trimetazidine, the results of echocardiography showed positive dynamics mainly in relation to the functional state of the heart (post-treatment results for such markers as IS, T ei LV, mR LA, T ei RV, FUP RV statistically significantly differed from pre-treatment results of these markers), as well as in relation to structural changes (results after treatment in OTC were significantly different compared to the results before treatment).

Conclusion

Thus, the study showed that patients with coronary artery disease have a violation of the structural and functional state of the myocardium, which were positively related (in terms of dysfunction) to the number of affected coronary arteries. Ischemic myocardial remodeling is characterized by dilatation of the chambers, an increase in the mass of the LV myocardium, impaired diastolic filling of the ventricles, a decrease in myocardial contractility, and an increase in pressure in the LA. And also, after additional treatment with trimetazidine, the results of EchoCG showed a positive trend mainly in relation to the functional state of the heart , as well as in relation to structural changes.

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