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Echocardiographic Results of Myocardial Revascularization Depending on the Genetic Polymorphism of Inflammatory Cytokines

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Introduction: Heart failure – is a clinical syndrome that occurs in response to systolic and/or diastolic myocardial dysfunction, leading to insufficient supply of tissues and organs with oxygen and nutrients. Cardiac fibroblasts are activated under conditions of increased mechanical stress, which is reflected in the dilation of the heart chambers. Under stress, they not only produce an excessive amount of extracellular matrix, but also increase the production of cytokines and stimulate the typical pathogenesis of inflammation.

The study of genes that control the activity of cytokines is one of the important tasks in uncovering the pathogenetic links of the initiation and course of diseases, and identifying predisposition to diseases in the early stages. Knowledge of their role in the pathogenesis of many diseases allows, on the one hand, to predict the risk of developing pathology or the severity of its course, on the other — to individually select specific therapy for a particular patient. It is known that with an unfavorable genetic background, in combination with environmental factors, a pathological phenotype is formed. And interleukin genes have an extremely high degree of polymorphism. So in what combination of genes is the most favorable course of the disease possible and in what case is it fleeting?

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Aims: To study the dynamics of the structural and functional state of the myocardium in patients with coronary heart disease during the first year after coronary revascularization, depending on the genetic polymorphism of proinflammatory cytokine genes
Study Design: Observational data.
Place and Duration of Study: Republican specialized scientific practical medical centre of therapy and medical rehabilitation, between January and December 2019.
Methodology: 127 patients with stable forms of coronary heart disease complicated by the development of chronic heart failure, who underwent coronary artery stenting, were examined. All patients were included in the study by echocardiography To assess the structural and functional state of the myocardium, and the genotype of the selected SNP genes IL-1, IL-6 and TNF-alpha with the allocation of minor alleles.
Results: The study showed a lower positive dynamics of the LV myocardial mass index in patients with the IL-6 minor allele and the right ventricular area reduction fraction and LV Tei in patients with the IL-1 minor allele. The TNF-alpha genotype had no significant effect on the processes of myocardial remodeling in CHD patients after revascularization. At the same time, for all three studied genes, a less favorable EchoCG characteristic was preserved during the entire follow-up period in patients carrying the minor allele.
Conclusion: Revascularization, which has an anti-ischemic effect, reduces the activity of the systemic inflammatory response, which explains the more pronounced positive dynamics of EchoCG indicators in patients with an initial high concentration of cytokines and a large number of minor alleles in the genotype of cytokine genes.

Keywords: Ischemic myocardial remodeling; genetic polymorphism of proinflammatory cytokines; coronary revascularization; tumor necrosis factor-alpha; interleukin-6; interleukin-1.

1. INTRODUCTION

Heart failure (HF) – is a clinical syndrome that occurs in response to systolic and/or diastolic myocardial dysfunction, leading to insufficient supply of tissues and organs with oxygen and nutrients. Cardiac fibroblasts are activated under conditions of increased mechanical stress, which is reflected in the dilation of the heart chambers. Under stress, they not only produce an excessive amount of extracellular matrix, but also increase the production of cytokines and stimulate the typical pathogenesis of inflammation.

The study of genes that control the activity of cytokines is one of the important tasks in uncovering the pathogenetic links of the initiation and course of diseases, and identifying predisposition to diseases in the early stages. Knowledge of their role in the pathogenesis of many diseases allows, on the one hand, to predict the risk of developing pathology or the severity of its course, on the other — to individually select specific therapy for a particular patient [1]. It is known that with an unfavorable genetic background, in combination with environmental factors, a pathological phenotype is formed. And interleukin genes have an extremely high degree of polymorphism [2]. So in what combination of genes is the most favorable course of the disease possible and in what case is it fleeting?

An increase in myocardial stress in CHF is associated with an increase in biomechanical strain. Mechano-sensitive adhesive proteins, including integrins and catherins, transform and translate mechanical signals between cells and their microenvironment and stimulate cellular response, including growth, differentiation, and inflammation [2]. TNF-α, IL-6, IL-18, and natriuretic pepdide (NUP) can be expressed by cardiomyocytes under conditions of increased mechanical stress [3]. Cyclic stress increases the expression of membrane receptors via the MAP kinase pathway [4], which mediates the induction of inflammatory cytokines by cardiomyocytes. Express pro-inflammatory cytokines, stimulating the transendothelial influx of monocytes into the myocardium. Also, cardiac fibroblasts (to a greater extent than cardiomyocytes) Express IL-1beta [5] under conditions of overextension, which induces leucopoiesis in the bone marrow and extramedullary foci of leucopoiesis [6].

Cytokines released during the activation of inflammation have an effect both locally-stimulating inflammation in the myocardium and the progression of CHF, and in distant tissues – the spleen and bone marrow, stimulating leucopoiesis and proliferation of reticuloendothelial tissue [7,8].

Systemic inflammation stimulates inflammation of the coronary endothelium, lipid per oxidation, decreased nitric oxide bioavailability, and increased cardiomyocyte apoptosis [9]. Inflammatory cytokines induce direct activation of cardiac immune resident cells, such as macrophages and B lymphocytes. B-lymphocytes are responsible for monocytic infiltration, which leads to non-classical myocardial dysfunction [10-12]. Autoimmune reaction is a known trigger of CHF and a risk factor for hospitalization and mortality in CHF patients [13-15]. Additional stimulators of autoimmune response are neurohumoral mechanisms of CHF regulation: renin-angiotensin-aldosterone system, sympathoadrenal system, natriuretic peptide, [16,17].

Genetic polymorphism of proinflammatory cytokines is associated with differences in effector function. This aspect of the specific features of pro-inflammatory status is being actively studied. One of the most studied proinflammatory cytokines is TNF-α. It causes endothelial dysfunction, reduces the contractility of myocytes, and contributes to the development of myocardial hypertrophy [18,19]. TNFA-308 GA / AA polymorphism predisposes to the development of dilated cardiomyopathy [20]. Il-4 variants −590CC, −33TT and-33CC are associated with an increased risk of ischemic cardiomyopathy, while variants-1098TG, -590 TC and – 33TC are associated with a low risk [21,22].

2. MATERIALS AND METHODS

We examined 127 patients with stable forms of coronary heart disease complicated by the development of chronic heart failure, who were inpatient treatment at the Republican specialized scientific and practical center of therapy and medical rehabilitation, who underwent coronary artery stenting according to the results of coronary angiography (CAG).

The study included patients of both sexes: men and women, aged 40 to 82 years (mean age 60.73 ± 9.86 years). The diagnosis of CHD was established on the basis of the clinical picture of the disease, anamnesis and data of clinical and instrumental research methods. Signs of chronic heart failure of functional class III-IV (FC) according to NYHA were detected in accordance with national recommendations for the diagnosis and treatment of CHF [2]. The duration of the disease was 8.7±3.56 years. All patients underwent coronary angiography (CAG) and indications for myocardial revascularization were determined. Indications for revascularization were determined collectively together with a cardiologist and a cardiac surgeon.

Basic therapy included (in an individually selected dosage) beta-blockers (bisoprolol or carvedilol)/ivabradine, angiotensin converting enzyme inhibitors (ramipril or perindopril)/anotensin receptor blockers (valsartan or telmisartan), aldosterone antagonists (spironolactone or eplerenone), an antiplatelet agent (aspirin or clopidogrel), an acetyl-CoA reductase inhibitor (atorvastatin or rosuvastatin). Also, according to the indications, patients took anticoagulants (neodicumarin or rivaroxaban), antiarrhythmic drugs (amiodarone), loop diuretics (furasemide or torasemide), cardiac glycosides (digoxin), etc.

The duration of follow-up was 12 months, between January and December 2019.

The criteria for inclusion in the study were the presence of patients with CHF of stages II-III and I–IV FC, a myocardial infarction not earlier than 6 months before inclusion in the study and

Exclusion criteria:

1) The presence of a myocardial infarction within the last 6 months.
2) Contraindications to CAG and endovascular revascularization
3) The presence of concomitant pathology of the heart-congenital and acquired heart defects.
4) The presence of severe concomitant somatic pathology.

All patients were included in the study by echocardiography to assess the structural and functional state of the myocardium, and the genotype of the selected SNP genes IL-1, IL-6 and TNF-alpha with the allocation of minor alleles. At the end of the year of follow-up, patients with CHD underwent control echocardiography to assess the dynamics of myocardial remodeling and progression of CHF, depending on the management tactics of patients and the genotypes of the studied cytokines.

Echocardiography was performed on a Samsung Medison ultrasound device "Accuvix V20"

(Korea) using a sector sensor with color mode and pulse-wave, continuous-wave mode with a frequency of 2-4 MHz in standard echocardiographic positions in M-and B-modes according to the recommendations of the American echocardiographic society (AES) (Schiller N. B. et al. 1989).

The structural parameters of remodeling were recorded as:

- End diastolic LV volume (Simpson's method) indexed to body surface area;
- End systolic volume of the left atrium (Simpson's method), indexed to the body surface area;
- End diastolic area of the right ventricle (planimetric method in the apical 4-chamber position), indexed to the body surface area;
- End systolic area of the right atrium (planimetric method in the apical 4-chamber position), indexed to the body surface area;
- Diastolic thickness of the interventricular septum (parasternal position along the long axis of the left ventricle, interventricular septum);
- Diastolic thickness of the posterior LV wall (parasternal position along the long axis of the left ventricle, posterior LV wall);
- LV myocardial mass ("shell" method, apical position), indexed to the body surface area;
- Sphericity index – the ratio of the short diameter of the LV to the length of the cavity.

Functional characteristics of the myocardial state:

- LV ejection fraction – the ratio of LV stroke volume (the difference between the final LV diastolic volume and the final LV systolic volume determined by the Simpson method) to the final LV diastolic volume;
- Index of violation of regional LV contractility – the average value of the point assessment of regional contractility using a 17-segment scheme. The assessment of segment contractility is five-point (0-hyperkinesis – systolic thickening more than 100%, 1-normokinesis – systolic thickening 50-100%, 2-hypokinesis-systolic thickening less than 50%, 3-akinesis-no systolic thickening, 4-dyskinesis – systolic bulging of the myocardial segment);
- Fraction of shortening square RV is the ratio of the difference of end-diastolic and end-systolic RV area measured by planimetric techniques in the apical 4-chamber position, to the end-diastolic area RV;
- Impact index – the impact volume of the LV, indexed to the surface area of the body;
- Minute index (MI) – the product of the impact index on the heart rate;
- Type of myocardial diastolic filling (dopplerography of transmitral and transtricuspid blood flow, classification of diastolic filling types according to the canadian classification of diastolic dysfunction, DD);
- Integral index of myocardial function (Tei – the ratio of the duration of closed valve periods to the period of expulsion (Doppler blood flow);
- Mean pulmonary artery pressure – was determined by the ratio of the duration of the period of acceleration of the expulsion flow to the total duration of the expulsion period on the pulmonary artery valve.

By agreement with the center for Advanced technologies under the Ministry of Innovative development of the Republic of Uzbekistan, molecular genetic studies were conducted in the laboratory of Biotechnology to study polymorphism-the TNF-α gene (863C>A), the IL-6 gene (174 G>C), the IL gene, the NUP - NPPB gene. The genotype was determined by polymerase chain reaction.

The material for DNA was venous blood from the ulnar vein with a volume of 1 ml. For the collection, storage and transportation of blood, disposable plastic tubes with a volume of 2.5 ml with an anticoagulant (preservative) of 0.5 ml were used. Blood for further processing was stored at a temperature of at least +4 ° C. The sequencing reaction of PCR products was performed using the Bigdye ® Terminator v3.1 kit from AppliedBiosystems. The principle of sequencing using BigDye sets is based on the use of fluorescently labeled bases acting as terminators and a cyclic sequencing reaction. Statement of the cyclic sequencing reaction by the Big Dyex Terminator v set.3.1 CycleSequencingKit (AppliedBiosystems, USA). Real-time PCR (or quantitative PCR,English Real-time PCR, qPCR, qRT-PCR) is a method

based on the polymerase chain reaction method, used to simultaneously amplify and measure the amount of a given DNA molecule. The main difference is that the amount of amplified DNA is measured in real time after each amplification cycle. For quantitative determination, two methods are used — fluorescent dyes that intercalate into double-stranded DNA molecules, and modified oligonucleotides (DNA probes) that fluoresce after hybridization with complementary DNA sites. Thus, the combination of amplification and detection stages in the real-time PCR method can significantly increase the reliability of PCR analysis, eliminating the possibility of contamination. The DNA supernatant was further subjected to PCR amplification. PCR analysis was performed using a set of reagents for PCR-RT DNA amplification GenePak ™ PCR Core (LLC “Laboratory isogen"). Master Mix tubes ready for amplification were used, which contain in the lyophilized dry state inhibited Taq DNA polymerase, deoxynucleose triphosphates and magnesium chloride with final concentrations, respectively, 1 u, 200 microns and 2.5 mm, as well as an optimized buffer system for standard PCR amplification. 2 mixtures were made, separately for each probe (WT and Mut). Master Mix tubes were filled with 2 µl of primer mixture with a final concentration of 0.5 µm, 10 µl of PCR solvent, 1 (1.2) µl of WT (Mut) fluorescent probe, and 1.5 µl of test DNA. For PCR amplification, a Real-Time PCR System 7500 (Applied Biosystems) amplifier was used. The amplification program included 5 minutes of pre-denaturation at 95 °C, 45 cycles: 94 °C-15 seconds, 54 °C-45 seconds. The results of real-time PCR are visualized in graphical form. The abscissa axis indicates the number of cycles performed, and the ordinate axis indicates the fluorescence intensity of the TaqMan probe. PCR amplification products were visualized in 2 % agarose gel for 30 min at 120 V and documented in UV light. The genotypes of the studied polymorphisms were analyzed by treating PCR products containing a single-nucleotide polymorphism with appropriate restrictases.

All data obtained during the study were recorded in Excel 2013 pivot tables. Arithmetic averages and their standard errors were used as characteristics of groups. The reliability of the intergroup difference was evaluated using the Student's unpaired test, the reliability of the difference in indicators recorded at the beginning and at the end of the observation period in the groups was determined using the Student's paired test. Differences were considered significant at $p<0.05$ (95% probability). The relative dynamics indicator was defined as the ratio of the absolute ratio in the observation period to the starting value of the index, expressed as a percentage (with a positive value of the relative dynamics of the index for the observation time increased, while a negative amount is decreased). When describing the dynamics in the observation groups, the arithmetic mean of the relative dynamics and its standard error were also calculated.

3. RESULTS AND DISCUSSION

Isolation of a group of patients carrying the minor allele of the IL-6 gene showed that in both groups of patients there was a decrease in the left ventricular mass index, however, with initially comparable values of LVMI, in patients with homozygous major allele of the IL-6 gene, there was a significantly greater decrease in the indicator compared to carriers of the minor allele (-6.84±1.00% vs. -0.66±1.57%, p<.01). At the same time, over the past year since revascularization, patients with homozygous major allele showed a significant decrease in LVMI (p<.001 with baseline data), while carriers of the minor allele showed no significant dynamics of LVMI (differences with baseline data-nd). As a result, in the group homozygous for the major alleles of the gene IL-6 by the end of the observation period achieved significantly lower value LVMI compared to carriers of the minor alleles (p<0.01 significant differences between groups at the end of the observation period).

For the rest, patients carrying the minor allele of the IL-6 gene were initially characterized by more pronounced pathological structural and functional remodeling of the myocardium, which was confirmed by less favorable indicators of SBP, DBP, heart rate, initial end diastolic LV volume, initial left atrium, initial right atrium, LV EF, mean pulmonary artery pressure. Endovascular revascularization contributed to a significant improvement in EchoCG parameters, more pronounced in the group of carriers of the minor allele (the significance of the difference in relative dynamics was established for SAD-p<.001, DBP-p<.001, initial end diastolic LV volume -p<.001, initial left atrium -p<.001, initial right atrium - p<.01, LVEF-p<.05). As a result, by the end of the observation period, the structural and geometric parameters of remodeling retained their difference between the groups initial end diastolic LV volume -p<.001, initial left atrium - p<.001, initial right atrium - p<.01), while the

value of the functional components of remodeling (LV EF, mean pulmonary artery pressure) groups were equal.

Carriers of the minor allele of the IL-1 gene initially differed in more pronounced pathological remodeling, which was manifested in significantly less favorable values of DBP (p<.01 significance of the difference in the initial value between the groups depending on the IL-1 genotype), IMLF (p<0.05), sphericity index (p<.001), LV EF (p<.001), regional contractility disorder index (p<.001), LV Tei (p<.001) and mean pulmonary artery pressure (p<.001). After revascularization

Table 1. Annual dynamics of echocardiographic parameters in patients with coronary heart disease after percutaneous coronary intervention, depending on the presence of a minor allele of the IL-6 gene (in the numerator-major homozygotes (n=96), in the denominator – heterozygotes and minor homozygotes (n=31)

Parameter	Initial	12 month later	Relative dynamics (%)
SAP, mmHg	128,44±2,66	121,98±1,06*	-1,49±2,06
	108,71±3,90^^^	123,87±1,75**	18,30±4,50^^^
DAP, mmHg	83,54±2,09	78,65±0,87*	0,03±2,84
	65,16±4,37^^^	77,74±1,35*	31,16±6,47^^^
Heart rate, BMP	94,32±2,33	68,48±0,93***	-22,47±2,50
	114,23±4,87^^^	71,06±1,69***	-30,99±5,73
iEDLV	75,13±1,44	72,40±0,80*	-1,44±1,53
	99,32±1,72^^^	80,58±1,62***^^^	-18,59±1,54^^^
iLA, ml/m^2	45,47±1,26	43,15±0,82***	-2,49±1,31
	67,77±2,84^^^	52,13±1,71***^^^	-20,97±2,58^^^
iRA, cm^2/m^2	10,79±0,27	10,86±0,26	1,93±1,64
	13,87±0,46^^^	13,06±0,51*^^^	-5,74±2,10^^
iRV, cm/m^2	18,81±0,40	18,42±0,38*	-1,60±0,80
	19,90±0,74	19,06±0,71*	-3,77±1,56
IVS, mm	10,69±0,15	10,72±0,15	0,47±0,51
	9,97±0,18^^	10,13±0,19^	1,68±0,99
LV posterior wall, mm	10,22±0,15	10,20±0,15	-0,15±0,29
	10,16±0,34	10,19±0,33	0,54±0,86
LVMI, g/m^2	136,78±4,46	124,77±3,54***	-6,84±1,00
	147,03±5,33	144,94±4,80^^	-0,66±1,57^^
LV sphericity index	0,66±0,01	0,64±0,01***	-3,01±0,66
	0,70±0,02	0,64±0,01***	-6,68±1,57^
LV EF, %	51,00±0,64	54,64±0,62***	8,01±1,21
	46,26±2,04^	53,55±1,42***	23,72±7,41^
index of local contractility	1,51±0,04	1,37±0,03***	-7,20±1,44
	1,58±0,08	1,36±0,05**	-10,22±3,05
RVFAC, %	35,08±0,84	36,11±0,76**	4,93±1,97
	33,77±1,59	35,48±1,34*	8,28±4,04
Impact Index, ml/m^2	38,05±0,79	39,48±0,59*	6,16±1,80
	45,33±1,91^^	43,06±1,42^	0,10±5,70
CI, ml/m^2	3628,35±135,14	2703,60±55,78***	-17,74±2,95
	5103,46±291,22^^^	3045,79±114,09***^^	-32,78±5,28^
DD LV, type	1,52±0,09	1,51±0,08	2,58±2, 47
	1,40±0,15	1,40±0,14	10,0±9,54
DD RV, type	0,76±0,09	0,77±0,09	-3,88±2,16
	0,50±0,14	0,40±0,09^	-8,33±4,23
Tei LV	0,50±0,01	0,49±0,01**	-2,61±0,72
	0,54±0,02	0,54±0,02	-0,38±0,31^
Tei RV	0,49±0,01	0,48±0,01	-1,01±0,52
	0,46±0,01	0,45±0,01*^	-3,19±1,07
Mean pulmonary artery pressure, mmHg	22,45±0,41	20,90±0,33***	-6,02±0,95
	27,52±0,68^^^	25,65±0,64**^^^	-6,17±1,87

** - reliability of the difference between the indicators and the initial data, ^ - reliability of the difference with homozygotes for the major IL-6 allele. One character – p<.05, two characters-p<.01, three characters-p<.001*

Table 2. Annual dynamics of EchoCG parameters in patients with CHD after percutaneous coronary intervention depending on the presence of the minor allele of the IL-1 gene (in the numerator-major homozygotes (n=97), in the denominator – heterozygotes and minor homozygotes (n=30)depending on the presence of the minor allele of the IL-1 gene (in the numerator-major homozygotes (n=97) , in the denominator – heterozygotes and minor homozygotes (n=30)

Parameter	Initial	12 month later	Relative dynamics (%)
SAP, mmHg	121,34±2,36	121,86±1,06	4,10±2,27
	131,00±6,24	124,33±1,72	0,89±4,57
DAP, mmHg	75,57±2,10	77,53±0,87	10,55±3,34
	90,33±4,73^^	81,33±1,17^	-1,83±5,63
Heart rate, BMP	99,97±2,42	68,90±0,90***	-26,64±2,23
	96,63±5,50	69,80±1,93***	-17,79±6,89
iEDLV	80,70±1,56	74,28±0,88***	-5,77±1,49
	82,10±3,81	74,77±1,76*	-5,14±3,38
iLA, ml/m^2	49,90±1,52	44,63±0,86***	-6,89±1,57
	54,20±3,66	47,63±2,02**	-7,33±2,78
iRA, cm^2/m^2	11,49±0,31	11,31±0,29	-0,43±1,43
	11,70±0,48	11,70±0,46	1,62±3,53
iRV, cm/m^2	19,22±0,43	18,66±0,40**	-2,35±0,90
	18,63±0,62	18,30±0,56	-1,42±0,88
IVS, mm	10,59±0,14	10,62±0,13	0,36±0,33
	10,27±0,31	10,43±0,29	2,08±1,62
LV posterior wall, mm	10,33±0,17	10,29±0,16	-0,33±0,28
	9,80±0,26	9,90±0,26	1,17±0,89
LVMI, g/m^2	134,12±3,94	125,58±3,31***	-4,89±1,00
	155,97±7,92^	143,00±6,43**^	-6,77±1,85
LV sphericity index	0,64±0,01	0,62±0,01***	-3,06±0,69
	0,76±0,02^^^	0,71±0,02***^^^	-6,65±1,43^
LV EF, %	51,79±0,55	55,48±0,56***	7,89±1,18
	43,53±2,08^^^	50,77±1,51***^^	24,63±7,64^
index of local contractility	1,39±0,03	1,32±0,02***	-3,72±0,99
	2,00±0,07^^^	1,53±0,07***^^	-21,57±3,61^^^
RVFAC, %	35,07±0,92	36,55±0,80***	7,15±2,29
	33,77±1,04	34,07±0,99	1,20±1,20^
Impact Index, ml/m^2	41,61±0,85	41,19±0,64	1,36±1,72
	34,07±1,60^^^	37,63±1,15^^	15,42±5,72^
CI, ml/m^2	4218,92±156,35	2838,47±58,36***	-24,97±2,82
	3243,12±232,39^^^	2621,10±109,49*	-9,91±6,00^
DD LV, type	1,29±0,07	1,33±0,07	6,96±3, 53
	2,16±0,17^^^	2,00±0,17^^	-5,33±2,88^
DD RV, type	0,62±0,09	0,59±0,08	-4,17±2,11
	1,00±0,13^	1,04±0,13^	-5,26±4,19
Tei LV	0,49±0,01	0,47±0,01**	-2,20±0,63
	0,58±0,02^^^	0,57±0,02^^^	-2,13±1,34
Tei RV	0,48±0,01	0,47±0,01	-0,76±0,46
	0,52±0,02	0,50±0,02*	-3,52±1,30
Mean pulmonary artery pressure, mmHg	22,80±0,41	21,55±0,38***	-4,95±0,89
	26,53±0,90^^^	23,70±0,74***^	-9,62±2,04^

** - reliability of the difference between the indicators and the initial data, ^ - reliability of the difference with homozygotes for the major IL-1 allele. One character – p<.05, two characters-p<.01, three characters-p<.001*

during the year, LVMI, sphericity index, LVEF, regional contractility disorder index, and meandifference between groups at the end of the follow - up period, sphericity index - p<.001, LVEF - p<.01, regional contractility disorder index - p<.01, mean pulmonary artery pressure-p<.05). At the same time, the relative dynamics of the sphericity index, LVEF, regional

Table 3. Annual dynamics of echocardiographic parameters in CHD patients after percutaneous coronary intervention, depending on the presence of a minor allele of the TNF-alpha gene (in the numerator-major homozygotes (n=91), in the denominator – heterozygotes and minor homozygotes (n=36)

Parameter	Initial	12 month later	Relative dynamics (%)
SAP, mmHg	120,77±2,41	122,42±1,04	5,25±2,43
	130,83±5,45	122,50±1,85	-1,48±3,69
DAP, mmHg	79,01±2,07	79,01±0,84	6,99±3,30
	79,17±4,90	76,94±1,45	9,23±6,03
Heart rate, BMP	95,73±2,43	69,16±1,06***	-22,79±2,64
	107,92±4,77^	68,97±1,13***	-29,00±4,99
iEDLV	78,22±1,73	73,33±0,86***	-3,42±1,73
	88,14±2,55^^	77,08±1,65***^	-11,20±1,88^^
iLA, ml/m^2	48,71±1,79	43,63±0,95***	-5,59±1,77
	56,47±2,15^^	49,67±1,37***^^^	-10,55±1,65^
iRA, cm^2/m^2	11,27±0,32	11,11±0,30	-0,20±1,61
	12,22±0,44	12,14±0,42^	0,71±2,65
iRV, cm/m^2	19,04±0,44	18,47±0,40**	-2,38±0,84
	19,17±0,62	18,83±0,62	-1,51±1,38
IVS, mm	10,47±0,15	10,60±0,15*	1,38±0,58
	10,61±0,26	10,50±0,23	-0,79±0,62^
LV posterior wall, mm	9,96±0,16	9,97±0,16	0,19±0,36
	10,83±0,28^^	10,78±0,27^	-0,42±0,59
LVMI, g/m^2	124,22±3,69	118,66±3,13***	-3,27±0,83
	177,36±4,54^^^	157,58±4,52***^^^	-10,54±2,04^^
LV sphericity index	0,66±0,01	0,63±0,01***	-4,02±0,75
	0,70±0,02	0,67±0,01**^	-3,61±1,24
LV EF, %	51,03±0,79	55,46±0,58***	11,82±2,74
	46,83±1,41^	51,61±1,34***^	11,90±2,64
index of local contractility	1,47±0,04	1,33±0,03***	-6,72±1,48
	1,68±0,08^	1,46±0,06***	-11,00±2,72
RVFAC, %	34,10±0,91	35,48±0,81***	6,49±2,22
	36,44±1,24	37,17±1,07	3,87±2,89
Impact Index, ml/m^2	39,34±0,90	40,61±0,61	6,94±2,47
	41,05±1,68	39,70±1,33	-1,03±2,70^
CI, ml/m^2	3771,02±140,08	2815,28±64,06***	-18,57±2,89
	4537,95±309,30^	2715,96±86,20***	-28,59±5,63
DD LV, type	1,38±0,08	1,36±0,08	3,21±2,52
	1,78±0,16^	1,78±0,15^	6,41±8,61
DD RV, type	0,74±0,09	0,74±0,09	-2,57±2,00
	0,66±0,16	0,63±0,13	-11,11±4,74
Tei LV	0,50±0,01	0,49±0,01**	-2,27±0,63
	0,53±0,02	0,52±0,02	-1,90±1,35
Tei RV	0,49±0,01	0,48±0,01**	-1,60±0,60
	0,47±0,02	0,46±0,01	-0,92±0,60
Mean pulmonary artery pressure, mmHg	22,95±0,49	21,13±0,39***	-6,85±1,06
	25,56±0,62^^	24,39±0,53**^^^	-4,03±1,26

** - reliability of the difference between the indicators and the initial data, ^ - reliability of the difference with homozygotes for the major TNF-alpha allele. One character – p<0.05, two characters-p<0.01, three characters-p<0.001.*

contractility disorder index, and mean pulmonary artery pressure was more pronounced in carriers of the minor allele (p<.05 for LVEF, sphericity index, and mean pulmonary artery pressure, and p<0.001 for the regional contractility disorder index).

Significant differences in the dynamics of remodeling indicators depending on the IL-1 genotype were found in relation to the fraction of reduction in the area of the right ventricle, which was comparable at the initial examination. After revascularization, the right ventricular area reduction fraction significantly increased in patients with homozygous major allele (+7.15±2.29%, p<.001 confidence with baseline values) and did not change in patients with minor allele carriers (1.20±1.20%, nd with baseline values, p<.05 confidence of the difference in relative dynamics between groups). Also, the LV Tei index significantly decreased in the group of homozygotes for the major allele of the IL-1 gene (p<.01) and did not change in carriers of the minor allele (differences in relative dynamics between groups – nd).

The selection of patients depending on the genotype of the TNF-alpha gene revealed significant differences in relative dynamics for the initial end-diastolic LV volume, the initial left atrium, and the LVMI: the dynamics was more significant in patients carrying the minor allele (p<0.01 significance of the difference in relative dynamics for the initial end-diastolic LV volume and the LVMI, p<0.05 for the initial left atrium). For the remaining echocardiographic parameters, there were no differences in dynamics during the year after revascularization between the groups. Initially, less favorable characteristics of the structural and functional state of the myocardium in patients with a minor allele – BP, LVL, posterior wall of the left ventricle, LVEF, index of regional contractility disorders, mean pressure in the pulmonary artery, remained different at the end of the follow-up period.

4. CONCLUSION

Thus, the study of the dynamics of myocardial remodeling in patients with ischemic heart disease during the year after endovascular revascularization of the presence of the minor alleles of proinflammatory cytokines have shown less positive dynamics indexed myocardial mass of left ventricle in patients-carriers of minor alleles of the gene IL-6 and the fraction of reduction of the RV, Tei RV and LV in patients-carriers of minor alleles of the gene IL-1. The genotype of the TNF-alpha a significant influence on the processes of myocardial remodeling in patients with IHD after revascularization is not provided. At the same time, for all three studied genes, a less favorable Echo CG characteristic was preserved during the entire follow-up period in patients carrying the minor allele.

A comparison of the cytokine status and the structural and functional state of the myocardium indicates the pathogenetic role of inflammation in the development of ischemic cardiomyopathy. Revascularization, which has an anti-ischemic effect, reduces the activity of the systemic inflammatory response, which explains the more pronounced positive dynamics of echocardiographic parameters in patients with an initial high concentration of cytokines and a large number of minor alleles in the genotype of cytokine genes.

CONSENT

As per international standard or university standard, participant's informed consent to participate in the study.has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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