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# Features of chronic heart failure depending on the left ventricular ejection fraction

Dushina A. G., Lopina E. A., Libis R. A.

**Aim.** To assess clinical and demographic data, structural and functional features of the myocardium in patients with chronic heart failure (CHF) with a preserved ejection fraction in comparison with patients with CHF with an intermediate (CHFinEF) and a reduced ejection fraction (CHF-rEF).

**Material and methods.** The study included 186 patients with CHF I-IIB stages, I-III functional classes. One hundred and three patients had a preserved ejection fraction (EF) (≥50%), 43 — intermediate (40-49%) and 40 — reduced (<40%). All patients underwent a comprehensive clinical examination, as well as standard echocardiography.

**Results.** Among patients with CHF-rEF, remodeling of the left ventricular myocardium by the type of concentric hypertrophy was more often observed (69,9%), and among CHF-inEF and CHF-nEF patients — by the type of eccentric hypertrophy (88,4 and 87,5%, respectively). Restrictive diastolic dysfunction was observed in 2,0% of patients with CHF-rEF and in 21,7% of patients with EF less than 50%.

**Conclusion.** The severity of the clinical course of CHF does not depend on the left ventricular EF. Epidemiology and etiology of CHF-rEF has fundamental differences from CHF-inEF and CHF-nEF. CHF-rEF is more common among women over 60 years old with arterial hypertension and obesity. For patients with CHF-inFV, myocardial remodeling by the type of concentric hypertrophy and the prevalence of non-restrictive types of diastolic dysfunction are characteristic.

**Key words:** chronic heart failure, ejection fraction.

**Conflicts of Interest:** nothing to declare.

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According to Russian Federal State Statistics Service, since the 2000s, an increase in the average life expectancy of both men and women has been observed. Despite the advances in medicine, the general population aging is inevitably associated with an increase in cardiovascular diseases and, as result, chronic heart failure (CHF). According to Russian epidemiological studies, CHF prevalence in the general population is 7% (overt heart failure — 4,5%), increasing from 0,3% in the age group of 20-29 years to 70% in people over 90 years of age [1]. According to the prognosis of Headenreich PA, et al. (2011), an increase of CHF prevalence by 25% is expected in the next 20 years [2].

To date, unified approaches to the treatment and management of all CHF patients was discredited. It is obvious that CHF population is not homogeneous, and in order to reduce mortality, disability and the number of hospitalizations due to CHF decompensation, a differentiated approach to healthcare organization is required.

It is important to separate CHF patients based on ejection fraction (EF), since there are various etiology and pathogenesis of the disease. Without understanding it, this is impossible to develop effective diagnostic algorithms and treatment methods. In 2016, the European Society of Cardiology issued Guidelines for the diagnosis and treatment of acute and CHF [3], where for the first time, in addition to patients with CHF with preserved (CHF-pEF) (⩾50%) and reduced (CHF-rEF) (<40%) EF, a category of patients with mid-range EF (CHF-mrEF) (40-49%) was added. This separation allowed specifying the imbalance of diagnostic, therapeutic and interventional capabilities among CHF patients. Regarding patients with CHF-rEF, a great number of large-scale clinical trials was conducted and therapeutic agents with proven efficacy can be used. However the population of patients with CHF-pEF and CHF-mrEF is still poorly understood and the prognosis is unfavorable.

The aim of the study was to evaluate the clinical and demographic data, structural and functional features of the myocardium in patients with CHF-rEF in comparison with patients with CHF-mrEF and CHF-pEF.

## Material and methods

The study included 186 patients with CHF of stage I-IIB (classification of Strazhesko M. D. and Vasilenko V. H.) and functional class (FC) I-III. Among this sample, 103 patients had a preserved ejection fraction (⩾50%), 43 — mid-range (40-49%) and 40 — reduced (<40%). The groups were comparable in stages and functional classes of CHF. The average age of the patients was 60,6±8,4 years. In 54 (29%) patients, CHF was a result of hypertension (HTN), in 132 (71%) — HTN in combination with coronary artery disease (CAD). A prerequisite for inclusion in the study, in addition to CHF, was a signed informed consent.

The study did not include patients with CHF which was a result of rhythm and conduction disturbances, congenital or acquired heart diseases and any inflammatory heart diseases (endocarditis, myocarditis, pericarditis). Patients with CHF decompensation (FC IV), history of acute coronary syndrome over the past three months, severe pulmonary, renal, hepatic pathology also did not include in the study.

After signing the informed consent, a complex examination was carried out for all patients. It included the collection of demographic and history data, physical examination with anthropometry, an assessment of the CHF severity (score of R. Cody, 1993 in V. Yu. Mareeva modification, 2000), one-dimensional, two-dimensional and Doppler echocardiography on the SonoScape 8000 (Korea).

During echocardiography, the following structural and functional parameters of the myocardium were evaluated: left ventricle (LV) EF (%), right ventricle (RV) dimension (mm), longitudinal dimension of right (RA) and left atrium (LA, mm), thickness of interventricular septum (IVS) and LV posterior wall (PW, mm), end-systolic (ESD) and end-diastolic (EDD) LV dimension (mm), LV volume parameters — end-diastolic (EDV) and end-systolic (ESV, ml). LV mass (LVM, g), left ventricular mass index (LVMI, g/m$^2$), and LV relative wall thickness (RWT, mm) were calculated using standard formulas. LV diastolic function was evaluated by transmitral blood flow.

The diagnosis of the main disease entities, including CHF, was established in accordance with current guidelines.

Statistical processing of the obtained data was carried out using Statistica 6.1 software (Statsoft.Inc, 2008). Qualitative characters are presented in the form of absolute and relative frequencies (n (%)); for quantitative characters having a normal distribution, the mean value and standard deviation (M±SD) were indicated. In the case of an abnormal distribution of a quantitative character, the median, upper and lower quartiles (Me [LQ;UQ]) were calculated. Comparison of quantitative characters with a normal distribution was carried out using parametric methods; in other

**Table 1**

**General characteristics of CHF patients depending on EF**

| Parameter | CHF-pEF (n=103) | CHF-mrEF (n=43) | CHF-rEF (n=40) |
|---|---|---|---|
| Age (years), M±SD | 60,4±7,4 | 61,1±11,3 | 60,6±6,7 |
| Gender (men/women), n (%) | 31 (30,1)/72 (69,9) | 32 (74,4)/11 (25,6) | 34 (85,0)/6 (15,0) |
| Etiology of CHF, n (%):<br>• HTN<br>• HTN+CAD | <br>46 (44,7)<br>57 (55,3) | <br>5 (11,6)<br>38 (88,4) | <br>3 (7,5)<br>37 (92,5) |
| Old myocardial infarction, n (%) | 15 (14,6) | 27 (62,8) | 27 (67,5) |
| Diabetes, n (%) | 19 (18,4) | 8 (18,6) | 6 (15,0) |
| Obesity (BMI), n (%):<br>• no<br>• I class<br>• II class<br>• III class | <br>28 (27,2)<br>38 (36,9)<br>25 (24,3)<br>12 (11,6) | <br>29 (67,4)<br>8 (18,6)<br>2 (4,7)<br>4 (9,3) | <br>25 (62,5)<br>9 (22,5)<br>5 (12,5)<br>1 (2,5) |

**Abbreviation:** BMI — body mass index.

**Table 2**

**Structural and functional myocardial characteristics in CHF patients depending on EF**

| Parameter | CHF-pEF (n=103) | CHF-mrEF (n=43) | CHF-rEF (n=40) | $p_{1-2}$ | $p_{1-3}$ | $P_{2-3}$ |
|---|---|---|---|---|---|---|
| EF, % | 66,0±7,6 | 44,2±3,4 | 32,6±3,6 | <0,01 | <0,01 | <0,01 |
| RV, мм | 31,7±2,8 | 30,7±4,6 | 32,8±4,7 | 0,26 | 0,53 | 0,18 |
| RA, мм | 50,4±4,4 | 52,2±7,6 | 54,7±7,6 | 0,41 | <0,01 | 0,19 |
| LA, мм | 51,6±6,8 | 53,9±10,7 | 58,7±12,4 | 0,27 | 0,04 | 0,23 |
| EDD, mm | 51,8±4,7 | 62,1±7,9 | 66,9±8,2 | <0,01 | <0,01 | 0,02 |
| ESD, мм | 33,1±5,1 | 48,9±5,4 | 55,3±8,2 | <0,01 | <0,01 | <0,01 |
| IVS, мм | 13,4±1,3 | 11,8±2,2 | 11,0±1,8 | <0,01 | <0,01 | 0,18 |
| PW, мм | 11,8±1,4 | 10,3±1,6 | 9,3±1,8 | <0,01 | <0,01 | 0,04 |
| RWT | 0,49±0,06 | 0,36±0,07 | 0,31±0,05 | <0,01 | <0,01 | <0,01 |
| EDV, мл | 130,1±26,9 | 198,7±54,2 | 234,8±64,0 | <0,01 | <0,01 | 0,02 |
| ESV, мл | 46,3±16,9 | 114,0±29,4 | 153,7±49,9 | <0,01 | <0,01 | <0,01 |
| EDVI, ml/m$^2$ | 67,4±11,8 | 100,3±22,1 | 120,8±34,2 | <0,01 | <0,01 | 0,02 |
| ESVI, ml/m$^2$ | 23,7±7,6 | 58,0±11,9 | 79,2±26,4 | <0,01 | <0,01 | <0,01 |
| Stroke volume, ml | 84,4±15,0 | 84,7±41,9 | 81,1±18,8 | 0,1 | 0,4 | 0,09 |
| LVM, g | 273,7±59,8 | 313,2±96,3 | 313,0±73,8 | <0,01 | 0,02 | 0,89 |
| LVMI, g/m$^2$ | 141,4±25,8 | 162,2±31,2 | 162,0±36,0 | <0,01 | <0,01 | 0,88 |

cases non-parametric methods were used. Differences were considered statistically significant if $p<0,05$.

## Results

The general characteristics of patients with CHF depending on EF are given in Table 1.

According to the presented data, women over 60 years old with HTN and overweight predominate among patients with CHF-pEF. CHF-mrEF and CHF-rEF are more common in men without obesity in the same age group. HTN, as the single CHF etiological factor, is rarely observed among patients with

**Table 3**

**Distribution of LV remodeling types in CHF patients depending on EF**

| Group / Type of remodeling | CHF-pEF (n=103) | CHF-mrEF (n=43) | CHF-rEF (n=40) |
|---|---|---|---|
| Concentric hypertrophy, n (%) | 72 (69,9) | 2 (4,6) | 1 (2,5) |
| Eccentric hypertrophy, n (%) | 18 (17,5) | 38 (88,4) | 35 (87,5) |
| Concentric remodeling, n (%) | 9 (8,7) | 3 (7,0) | 1 (2,5) |
| Normal model, n (%) | 4 (3,9) | 0 | 3 (7,5) |

EF less than 50%. However the proportion of patients with old myocardial infarction in this population increases sharply.

HTN (95,5%) and CAD (69,7%), as well as their combination (more than 50%), are the leading causes of CHF in Russia, Europe and United States [4, 5]. This is traced also in our study.

CHF symptoms and signs with the same prevalence were found in all groups. The most common clinical CHF manifestations were exertional dyspnea, pastosity, swelling of the feet and lower legs, palpitations, less often — congestive pulmonary rales, hepatomegaly.

An assessment of CHF severity (score of R. Cody, 1993 in V. Yu. Mareeva modification, 2000) also did not show differences between the groups: median in CHF-pEF group — 3,0 [3,0; 4,0] points, CHF-mrEF group — 3,0 [3,0; 4,0] points, CHF-rEF — 4,0 [3,0; 4,0] points ($p>0,05$).

The structural and functional myocardial parameters have a number of features depending on the EF. It implies the need for a differentiated approach to management of these patients (Table 2).

Table 2 shows that dilatation of the cardiac cavities is most outstanding in patients with reduced EF, thickness of LV walls — in patients with EF⩾50%. Patients with CHF-mrEF did not significantly differ from patients with CHF-rEF by the dimensions of the heart cavities, with the exception of lesser LV dilatation. By the extent of LV walls' thickening, patients with CHF-mrEF also had similar values with CHF-rEF patients. Differences of EDV and ESD were preserved between the groups even after indexing by body surface area.

Myocardial mass values and mass index increased with a decrease in EF less than 50%, however, with a further decrease in systolic function, significant differences between the groups were not obtained.

Based on the calculation of LVMI and LV RWT, LV geometric models (types of remodeling) were evaluated. According to the classification of Ganau A, et al. (1992), there are 4 types of structural and functional myocardial change: concentric hypertrophy, eccentric hypertrophy, concentric remodeling and the normal LV model [6]. According to the literature, patients with heart failure with the same provenance can have both concentric and eccentric LV hypertrophy [7]. The distribution of patients depending on the type of remodeling in the study groups is presented in Table 3.

Among patients with CHF-pEF, concentric hypertrophy was most common, while the vast majority of patients with CHF-mrEF and CHF-rEF had eccentric hypertrophy. High prevalence of concentric hypertrophy is characteristic of patients with CHF-pEF [8, 9] and is direct evidence of diastolic dysfunction [10], which plays a leading role in the development of this type of CHF. Volume overload and dilatation of heart cavities are more associated with the eccentric remodeling, which was observed in patients with EF less than 50%.

A number of studies have proved that LV concentric hypertrophy is the most unfavorable prognostic type of structural and functional myocardial change, which is associated with the greatest number of cardiovascular complications [11]. Thus, according to the literature [12, 13], risk of cardiovascular complications within 10 years in concentric LV hypertrophy is 30%, in eccentric hypertrophy — 25%, in concentric remodeling — 15%.

We also performed an analysis of echocardiographic parameters reflecting diastolic function. Noteworthy that there is diastolic dysfunction not only in patients with CHF-rEF, but also in the vast majority of patients with EF less than 50% [14]. In preserved EF, diastolic dysfunction predominates by hypertrophic type — 68 (66%) patients, less often by pseudonormal — 33 (32%) patients. As systolic dysfunction progresses, diastolic function worsens with an increase in the number of patients with restrictive type (21,7%) of diastolic dysfunction, which has the most unfavorable prognosis in patients with CHF [15].

## Conclusion

Thus, the severity of the clinical course of CHF does not depend on LVEF. The epidemiology and etiology of CHF-pEF has fundamental differences

from CHF-mrEF and CHF-rEF: CHF-pEF is more common among women over 60 with HTN and obesity. For patients with CHF-pEF, myocardial remodeling by concentric hypertrophy and the prevalence of non-restrictive types of diastolic dysfunction are characteristic.

**Conflicts of Interest:** nothing to declare

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# Expression of miRNA-27a in the serum of patients with non-ST elevation acute coronary syndrome who underwent percutaneous coronary intervention

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Coronary artery disease (CAD) is a multifactorial disorder. Previously have been identified genes whose polymorphic variants are associated with an increased risk of CAD. Genetic control of the development of CAD at the post-transcriptional level is carried out using step-wise and multicomponent regulation of gene expression with the participation of specific molecules called micro-ribonucleic acids (miRNAs). Currently, many authors consider these molecules, in particular miRNA-27a, as potential sensitive diagnostic markers for acute coronary syndrome (ACS).

**Aim.** To assess the level of miRNA-27a expression in the serum of patients underwent percutaneous coronary intervention (PCI) after non-ST elevation ACS.

**Material and methods.** Forty patients with non-ST elevation ACS who underwent coronary artery stenting were examined. The comparison groups consisted of 80 patients with a stable CAD who underwent coronary artery bypass surgery, and 20 patients without clinical signs of CAD operated due to valvular disorders without atherosclerotic lesions. All patients underwent coronary angiography. The expression level of miRNA-27a was determined in serum by real-time polymerase chain reaction.

**Results.** In patients with non-ST elevation ACS, who underwent PCI, the expression level of miRNA-27a in serum was higher than in patients without atherosclerotic lesions (6,99±1,69 and 3,05±0,89, respectively; p0,05).

**Conclusion.** High levels of miRNA-27a expression can be considered as a marker of coronary lesion severity in patients with CAD, but not as a marker for ACS.

**Key words:** micro-RNA, coronary artery disease, acute coronary syndrome.

**Conflicts of Interest:** nothing to declare.

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Cardiovascular diseases (CVD) and foremost coronary heart disease (CAD) are one of the most important medical and social problems due to its high share in the patterns of morbidity, disability and mortality. Despite the progress in primary prevention and pharmacotherapy, as well as the high efficiency of surgical methods for the CAD treatment, in particular percutaneous coronary interventions (PCI), today CAD is a leading cause of death worldwide. The annual incidence of acute coronary syndrome (ACS) in Europe remains high and varies from 1:80 to 1:170 people per year according to various registers. In this regard, there is a need to search for new molecular genetic markers of CAD (including ACS) severity.

The number of publications on this problem is constantly increasing. However, little is still known about the post-transcriptional regulation of the expression of CAD candidate genes. Post-transcriptional gene regulation is a change in the RNA structure until the start of gene translation. One of the main processes of post-transcriptional regulation is RNA interference. RNA interference is a process directed by special regulatory molecules — noncoding small interfering RNA — microRNA (miRNA) [1, 2].

It is known that miRNAs plays an important role in the CVD development by participating in various biological processes, such as endothelial dysfunction, cell adhesion, plaque formation and rupture, angiogenesis [3, 4], proliferation, metabolism, and apoptosis [5].

In recent years, special attention has been paid to the study of miRNA circulating in the blood, which can be used as markers for minimally invasive diagnosis of CVD, including some forms of CAD. So, it is known that a number of miRNA can be considered as ACS markers [6-8].

There are few contradictory studies about miRNA-27a, which associated with ACS [9-11].

In this regard, the aim of this study was to evaluate the level of miRNA-27a expression in blood serum in patients with non–ST-segment elevation ACS after PCI.

## Material and methods

The study was approved by the Local Ethics Committee of the First Pavlov State Medical University of St. Petersburg; all patients signed an informed consent.

The study included 40 people (28 men and 12 women) with CAD after PCI due to ACS. All patients underwent coronary angiography to determine the nature of coronary artery injury and management tactics. Patients were divided into 2 groups. The first group consisted of 19 patients (48%) with diagnosed one- or two-vessel CAD, the second group — 21 patients (51%) with multivessel CAD (3 arteries and more). The comparison group consisted of 20 (10 men and 10 women) subjects without CAD, according to coronary angiography.

Also, as an additional comparison group, 80 patients with a stable CAD (57 men and 23 women) and clinical picture of angina pectoris, which later underwent planned coronary artery bypass grafting (CABG), were examined.

Exclusion criteria were previous CABG, thyroid disease, secondary obesity and hypertension, oncology, acute kidney injury and chronic kidney disease, systemic connective tissue diseases, infective endocarditis, hypo/hyperthyroidism, organic brain diseases, alcoholism, drug addiction.

All patients with ACS received therapy in accordance with the guidelines for the management of ACS patients. The following data were collected from all patients: smoking history, family history of CVD, presence of overweight/obesity. A general examination was performed; height, body weight, waist circumference (WC) were measured and body mass index (BMI) was calculated. All biochemical parameters were determined on an automatic biochemistry analyzer (COBAS INTEGRA 400/700/800) with standard Roche kit (Germany). Quantitation of venous plasma glucose by hexokinase method was performed. Serum lipids (total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C)) was analyzed by enzymatic method.

Blood sampling was carried out no longer than 48 hours after the ACS onset and before CABG in patients with stable angina pectoris. Molecular genetic tests were performed at the Department of Clinical Laboratory Diagnostics of First Pavlov State Medical University of St. Petersburg. Blood serum was used in miRNA isolation. miRNA was isolated using the miRNeasy Mini Kit (QIAGEN, USA). The concentration of the miRNA aqueous solution was determined on a Nanodrop 1000 spectrophotometer (Thermo Scientific, USA). Reverse transcription was performed using a TaqMan miRNA reverse transcription kit. Real-time polymerase chain reaction was carried out using a miRNA-27a expression kit manufactured by Applied Biosystems (USA) TaqMan® Gene Expression Assays.

Statistical processing was carried out using the parametric and nonparametric methods. The level

of miRNA-27a had a normal distribution. Logarithm of miRNA determination results were taken to stabilize the dispersion and symmetrize the distribution law. The data are presented as an estimate of the arithmetic mean (M) and error of the mean (m). To assess the intergroup differences, the Wilcoxon-Mann-Whitney U test was used. When comparing frequency values, the Pearson's chi-squared test and Fisher's exact test were used. A multivariate regression analysis was performed to establish the association of miRNAs with a combination of various indicators potentially affecting it. The logarithmic miRNA was used as a dependent variable. Anamnestic, clinical, laboratory and functional parameters were used as independent explicative variables. For the diagnosis of multicollinearity, the VIF (variance inflation factor) was calculated and considered significant if it was less than two. Statistical processing was performed using SPSS 20.0 for Windows. The critical significance level of the null hypothesis (the absence of differences and influences) was taken equal to <0,05.

## Results

Patients with non-ST segment elevation ACS after PCI of groups 1A (one- or two-vessel CAD) and 1B (multivessel CAD), patients without coronary atherosclerotic lesions (comparison group 1) and patients with stable CAD (comparison groups 2A and 2B) were comparable in age (Table 1).

Among the modifiable CVD risk factors, smoking was the most common in the group of patients with ACS. Among patients with ACS, 62,5% of patients smoked, which is significantly more than among patients without CAD (p<0,05). The level of miRNA-27a expression in blood serum in smokers and non-smokers with ACS did not differ (p>0,05).

It was shown that 12,5% of patients with ACS had a positive family history of CVD; the level of miRNA-27a expression in blood serum in patients with/without this risk factor also did not differ (p>0,05).

Anthropometric parameters were analyzed in patients with ACS and comparison groups. Abdominal obesity (AO) was verified according to the criteria of the International Diabetes Federation (IDF, 2005). According to these criteria, AO were in 46% of men (n=13) and 42% of women (n=5). The average WC values in patients with ACS of 1A and 1B groups did not differ, but in men with ACS and stable CAD, WC was greater than in men without CAD (p<0,01) (Table 1). In women, such differences were not detected (p>0,05) (Table 1).

When assessing the level of miRNA-27a depending on AO presence/absence in men and women, WC was recalculated from a quantitative to qualitative character taking into account different standards for men and women. There were no significant differences in the level of miRNA-27a in patients with and without AO (p>0,05).

When assessing miRNA-27a level in patients with ACS in groups with normal body weight, overweight and class I-III obesity, there were no significant differences in miRNA27a level (p>0,05).

When assessing the serum lipid, it was found that TC and LDL-C levels in patients with ACS and patients with a stable CAD did not differ, but were lower than in patients without CAD (Table 1). Probably, these differences are due to the regular use of HMG-CoA reductase inhibitors in patients with CAD.

The expression level of miRNA-27a in men and women of groups 1A and 1B did not differ (p>0,05).

20% of patients with ACS had type 2 diabetes (T2D). It was found that the expression level of miRNA-27a in patients with CAD and T2D and without T2D did not significantly differ (p>0,05).

It was found that in patients with CAD after non-ST segment elevation ACS, and in patients with a stable CAD, the level of miRNA-27a expression in blood serum was higher than in patients without CAD (6,99±1,69 RU, 7,82±1,79 RU and 3,05±0,89 RU, respectively; p<0,05). Moreover, both patients with ACS and patients with stable CAD and multivessel coronary lesions had a higher level of miRNA-27a serum expression than patients with one- or two-vessel CAD (p<0,01) (Table 1).

At the same time, the level of miRNA-27a serum expression in patients with non-ST segment elevation ACS (groups 1A and 1B) and in patients with stable CAD (groups 2A and 2B) did not differ (6,99±1,69 RU and 8,57±3,90 RU, respectively; p>0,05).

A comparative analysis of miRNA-27a serum expression in patients with ACS revealed the following: in patients with hemodynamically significant stenoses of the diagonal branch of the left coronary artery and the posterolateral branch of the right coronary artery than patients with coronary artery stenosis less than 70%, higher levels of miRNA-27a expression (5,2±1,44 RU and

**Table 1**

**General characteristics and serum miRNA-27a expression level in participants**

| Parameter | Group 1A Patients with non-ST segment elevation ACS (one- or two-vessel lesion) n=19 (48%) | Group 1B Patients with non-ST segment elevation ACS (multivessel lesion) n=21 (52%) | Comparison Group 1 Patients without CAD n=20 | Comparison Group 2A Patients with stable CAD (one- or two-vessel lesion) n=29 (36%) | Comparison Group 2B Patients with stable CAD (multivessel lesion) n=51 (64%) | p |
|---|---|---|---|---|---|---|
| miRNA-27a, RU | 5,87±2,64 | 8,00±2,19 | 3,05±0,89 | 4,82±1,82 | 11,41±4,45 | $p_{1-1A;1-1B;1-2A;1-2B<0,05}$ $p_{1A-1B<0,01}$ $p_{2A-2B<0,01}$ |
| Age, years | 63,05±2,66 | 64,86±1,80 | 59,13±3,47 | 61,50±2,30 | 62,50±2,40 | NS |
| Waist circumference in men, cm | 105,53±3,57 | 104,58±4,44 | 95,32±4,37 | 99,80±3,90 | 100,80±4,20 | $p_{1-1A;1-1B;1-2A;1-2B<0,01}$ |
| Waist circumference in women, cm | 89,60±5,77 | 88,30±4,81 | 81,86±5,84 | 88,50±4,20 | 89,20±4,40 | NS |
| Body mass index, $kg/m^2$ | 28,02±1,17 | 28,70±1,27 | 25,44±1,08 | 28,40±1,90 | 28,30±1,80 | NS |
| Total cholesterol, mmol/l | 4,37±0,15 | 4,23±0,13 | 5,18±0,19 | 4,70±0,20 | 4,30±0,20 | $p_{1-1A;1-1B;1-2A;1-2B<0,001}$ |
| Low density lipoprotein cholesterol, mmol/l | 1,51±0,15 | 1,18±0,12 | 3,08±0,14 | 2,40±0,30 | 2,10±0,20 | $p_{1-1A;1-1B;1-2A;1-2B<0,001}$ |
| High density lipoprotein cholesterol, mmol/l | 1,27±0,09 | 1,28±0,06 | 1,26±0,14 | 1,10±0,10 | 1,10±0,10 | NS |
| Triglycerides, mmol/l | 1,78±0,16 | 1,65±0,13 | 1,20±0,16 | 1,80±0,20 | 1,90±0,10 | $p_{1-1A;1-1B;1-2A;1-2B<0,05}$ |
| Blood glucose, mmol/l | 5,89±0,18 | 6,47±0,32 | 5,41±0,34 | 5,80±0,20 | 5,90±0,20 | $p_{1-1A;1-1B;1-2A;1-2B<0,001}$ |

**Abbreviation:** NS — not significant.

9,33±3,10 RU, respectively; p<0,04; 1,58±0,51 RU and 7,76±1,90 RU, respectively; p<0,05) were detected.

When conducting a correlation analysis in ACS group, a positive correlation was found between miRNA-27a expression level and total number of implanted stents (r=0,327, p=0,04). Moreover, when performing multivariate regression analysis, the factor potentially affecting the serum miRNA-27a expression level was the number of implanted stents (p=0,001, VIF=1,03, r=0,42).

## Discussion

In recent decades, complex approach to the CVD diagnosis and treatment is most relevant; CAD as a multifactorial disease is no exception. According to modern concepts, the most important factors in the CAD development and progression are not only well-known cellular and biochemical markers, but also genetic and epigenetic factors. A special role among epigenetic factors is played by miRNA that regulate post-transcriptional gene expression. To date, more than 1800

human miRNAs are known and this list is constantly rising.

To date, a number of miRNAs are considered as new diagnostic and prognostic markers in patients with various CVDs. The use of such markers may become relevant and appropriate in clinical practice, taking into account the its relative simplicity and accessibility [12].

Despite a large number of studies about the miRNA-27a role in coronary artery atherosclerosis and stable CAD, there are few studies that evaluated miRNA-27a level in ACS. In the study by Shvangiradze TA, et al. (2016) [9], where only patients with a stable CAD and T2D were included, it was found that the miRNA-27a expression level was higher in the T2D and CAD group than in T2D patients without CAD. In our study, it was found that serum miRNA-27a expression level was higher in patients with a stable CAD and ACS than in those without atherosclerotic coronary lesions, which is consistent with the results of the study by Alvarez M, et al. [12] and other recent studies by Aranda JF, et al. [13] and Chen W-J, et al. [14].

Moreover, in our study, it was found that in multivessel CAD, the miRNA-27a expression level is higher than in one- and two-vessel lesions. In a study by Devaux Y, et al. [10] miRNA-27a prognostic significance in patients after ACS was evaluated. It was shown that an increased miRNA-27a expression level was associated with adverse clinical outcomes after myocardial infarction. That, according to the authors, may be due to a more severe coronary lesion in this category of patients. However, there are no publications on miRNA-27a expression level in multivessel and one- and two-vessel lesions.

In our study, no evidence was obtained indicating that miRNA-27a may be a marker of ACS. This is consistent with a study by Kukreja R, et al. [11].

During the correlation analysis, we revealed a positive correlation between the miRNA-27a level and total number of implanted stents. Moreover, multivariate regression analysis showed that the total number of implanted stents may be a factor potentially affecting miRNA-27a serum level. This suggests that miRNA-27a can take part in the neovascularization and endothelial dysfunction, including those associated with stenting. This is an important mechanism that is also being discussed when studying the miRNA-27a role in CAD patients after PCI. So, Veliceasa D, et al. [15], studied the miRNA-27b role, related to miRNA-27a, in an experimental ischemia model in mice and demonstrated that in critical ischemia miRNA-27b increase vascularization, decrease fibrosis, activate tissue revascularization and perfusion. The authors of this study suggest that these effects are possibly due to a decrease in the expression of delta-like protein 4, interleukin-10 and receptors activated by peroxisome proliferators.

## Conclusion

Based on the data obtained, it can be assumed that higher miRNA-27a expression level is associated with extended, clinically significant coronary atherosclerosis in patients with non-ST segment elevation ACS and in patients with stable CAD, but is not an ACS marker.

**Conflicts of Interest:** nothing to declare.

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# Bleeding risk factors in patients with acute coronary syndrome: data from observational studies ORACUL II

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**Aim.** To identify the risk factors for bleeding of BARC scale 2-5 types in patients after acute coronary syndrome (ACS).
**Material and methods.** The data of 1502 patients from the open multicenter study, ORACUL II, were used — 894 men (59,5%) and 608 women (40,5%), mean age — 65,7±12,9 years. Five hundred sixty (37,3%) patients had ACS with ST-segment elevation and 942 (62,7%) — ACS without ST-segment elevation. Bleeding was recorded in 164 patients (10,9%), including index admission — in 39 (2,6%) patients, of which severe (types 3-5) — 0,5%, significant — 1,7% (types 2-5).
**Results.** Within a year after discharge, bleeding was observed in 126 (8,4%) patients, large — 0,8%, significant — 2,4%. The development of bleeding type 2-5 was associated with the presence of gastric ulcer and duodenal ulcer, gastrointestinal bleeding in history, decreased creatinine, hemoglobin clearance, age of patients, the use of anticoagulants in the composition of triple or double antithrombotic therapy, conducting of percutaneous interventional procedures, the presence of heart failure 2-4 Killip class at admission. ROC analysis showed that the predictive value of the ORACLE bleeding risk scale is 0,762, sensitivity — 62%, specificity — 78%.
**Conclusion.** Thus, we based on routine clinical practice have created a simple scale for assessing the risk of bleeding in patients with ACS.

**Key words:** acute coronary syndrome, bleeding, BARC, mortality, ORACLE risk scale. Conflicts of Interest: nothing to declare.

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Large-scale implementation of interventional management for acute coronary syndrome (ACS) and the widespread use of modern antithrombotic therapy (ATT) have made safety an urgent problem. Every 10th patient after an ACS episode develops bleeding within 2 years; up to 4% suffers it during initial hospitalization [1-3]. According to some reports, over the past 10 years, the risk of in-hospital bleeding in such patients has increased 1,8 times. At the same time, those who suffered serious bleeding in a hospital have a higher risk of ischemic events, including fatal ones, at least during the next year [4]. The listed facts provided the basis for the concept of "avoiding" the bleeding risk. However, it has not been widely used in clinical practice. An essential part of this concept is the bleeding risk management, and therefore research in this area is still relevant.

The aim of this study was to identify risk factors associated with the development of bleeding in ACS patients in actual clinical practice.

## Material and methods

The present analysis is based on data obtained in the open-label observational multicenter study ORACUL II. The selection of patients was carried out in the period from 2014 to 2017. The inclusion criteria are described in detail in previous publications [5]. The rationale for inclusion in the study was the indications for percutaneous coronary interventions (PCI) in ACS patient, regardless of whether PCI was performed or not.

The presented analysis included data on 1502 patients who had at least 1 follow-up visit after discharge from the hospital. The exclusion criteria were no patient consent to take part in research or inability to contact the patient after discharge. The clinical characteristics of patients are presented in Table 1.

All patients received standard therapy based on current guidelines.

At follow-up visits (when discharged from the hospital, on day 25, 90, 180 and 360 from the inclusion), all cases of bleeding were recorded with a description of their nature, source, severity, management and classification according to the Bleeding Academic Research Consortium (BARC) scale [6]. Adverse outcomes were also recorded (death and its cause, repeated episodes of ACS, re-revascularization after discharge from the hospital, strokes and cases of complicated atherosclerosis). Pharmacological class, name and dose of drugs were also recorded.

The study was approved by the local ethics committees of the organizations participating in the study. All participants completed the informed consent.

Statistical data processing was performed using SPSS 23.0 and MedCalc 18.5 software. An analysis of the distribution and its normality was carried out. Mean values and standard deviation values (M±SD) were calculated. If the distribution was considered normal, Student's t-test was used to analyze the

**Table 1**

**Clinical characteristics of patients**

| Parameter | All patients (n=1502) |
|---|---|
| Men/Women (n, %) | 894 (59,5%)/608 (40,5%) |
| Age, years | 65,7±12,9 |
| BMI, kg/m$^2$ | 28,3±4,99 |
| STE-ACS/ NSTE-ACS, (n, %) | 560 (37,3%)/ 942 (62,7%) |
| History of CAD, (n, %) | 1132 (74,7%) |
| History of MI, (n, %) | 466 (31,5%) |
| History of HTN, (n, %) | 1320 (87,9%) |
| History of stroke, (n, %) | 164 (12,6%) |
| HF before current hospitalization, (n, %) | 769 (51,2%) |
| Class 2-4 by Killip, n (%) | 297 |
| Peripheral artery disease, (n, %) | 401 (26,8%) |
| Diabetes, (n, %) | 354 (23,6%) |
| COPD, (n, %) | 66 (4,3%0 |
| Asthma, (n,%) | 36 (2,3%) |
| Sleep Apnea, (n,%) | 30 (2,0%) |
| Gastroduodenal ulcer, (n, %) | 216 (14,3%) |
| History of GIB, (n, %) | 26 (1,7%) |
| Hepatic disorders, (n, %) | 95 (6,3%) |
| Thyroid disorders, (n, %) | 178 (11,8%) |
| History of anemia, (n, %) | 131 (8,7%) |
| History of kidney disease, (n, %) | 584 (38,8%) |
| History of cancer, (n, %) | 131 (8,7%) |
| Alcohol consumption, (n, %) | 672 (44,7%) |
| Smoking, (n, %) | 405 (26,9%) |
| History of CVD, (n, %) | 553 (36,8%) |

**Abbreviations:** BMI — body mass index, STE-ACS — ST segment elevation ACS, NSTE-ACS — non-ST segment elevation ACS, CAD — coronary artery disease, MI — myocardial infarction, HTN — hypertension, HF — heart failure, COPD — chronic obstructive pulmonary disease, GIB — gastrointestinal bleeding, CVD — cardiovascular disease.

**Table 2**

**The source and severity of bleeding recorded at different follow-up visits**

| | Discharge | Day 25 | Day 90 | Day 180 | Day 360 |
|---|---|---|---|---|---|
| Number of patients with bleeding | 39 | 39 | 31 | 41 | 45 |
| Source | | | | | |
| GIB | 8 | 7 | 4 | 4 | 8 |
| Hemorrhoids | 1 | 4 | 1 | 1 | 2 |
| Paracentesis-induced bleeding | 19 | 1 (CABG) | | | |
| Spontaneous subcutaneous hematomas | 2 | 1 | 1 | 1 | 2 |
| Hematuria | 3 | 1 | 3 | 5 | 2 |
| Nosebleeds | 1 | 20 | 15 | 20 | 22 |
| Uterine bleeding | | 1 | 1 | 1 | 1 |
| Bleeding gums | | 2 | 1 | 7 | 6 |
| Hemopericardium | 1 | | | | |
| Aortic dissection | 1 | | | | |
| Intracranial bleeding | | | 1 | | |
| Postoperative bleeding | | | 1 (CABG) | 1 | |
| Hemoptysis | | | | 1 | |
| Unspecified source | 3 | 2 | 1 | | 2 |
| Severity by BARC classification | | | | | |
| Type 1<br>Type 2<br>Type 3<br>Type 4<br>Type 5 | 12<br>18<br>8<br><br>1 | 30<br>5<br>3<br>1<br> | 19<br>8<br>1<br>1<br>2 | 34<br>6<br>1<br><br> | 36<br>5<br>2<br><br>2 |

**Abbreviations:** GIB — gastrointestinal bleeding, BARC — Bleeding Academic Research Consortium.

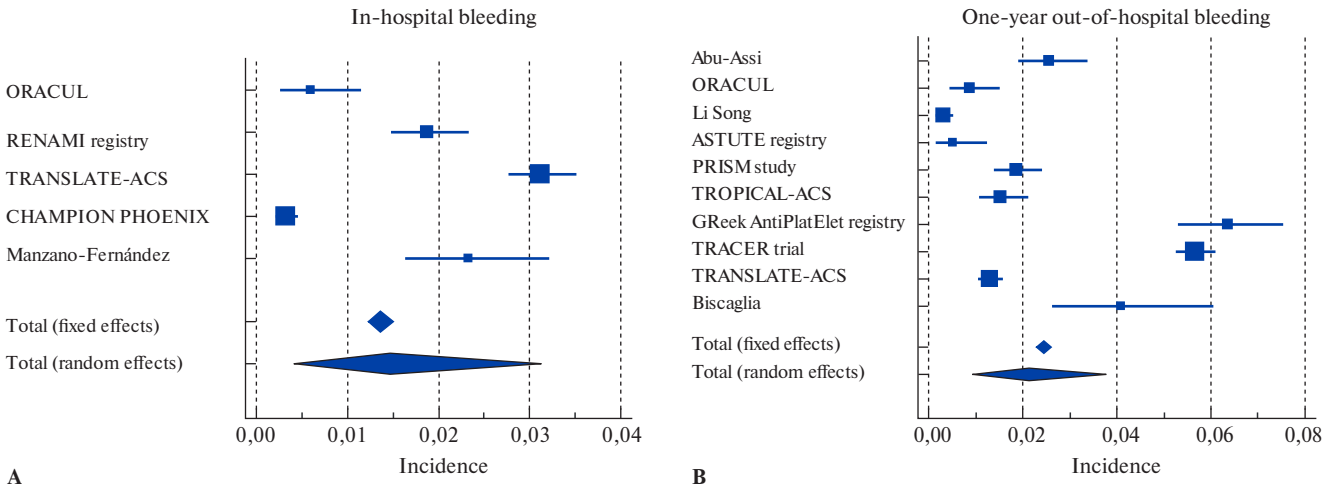


**Fig. 1 (A, B).** A meta-analysis of the incidence of in- (A) and out-of-hospital (B) bleeding in patients after ACS.

significance of differences; non-parametric methods were used in cases of non-normal distribution. Discrete values were compared by Pearson's chi-squared test.

To assess the bleeding incidence in comparison with literature data, a meta-analysis of research data published in 2015-2018 was carried out. A literature search was conducted using PubMed with the key-

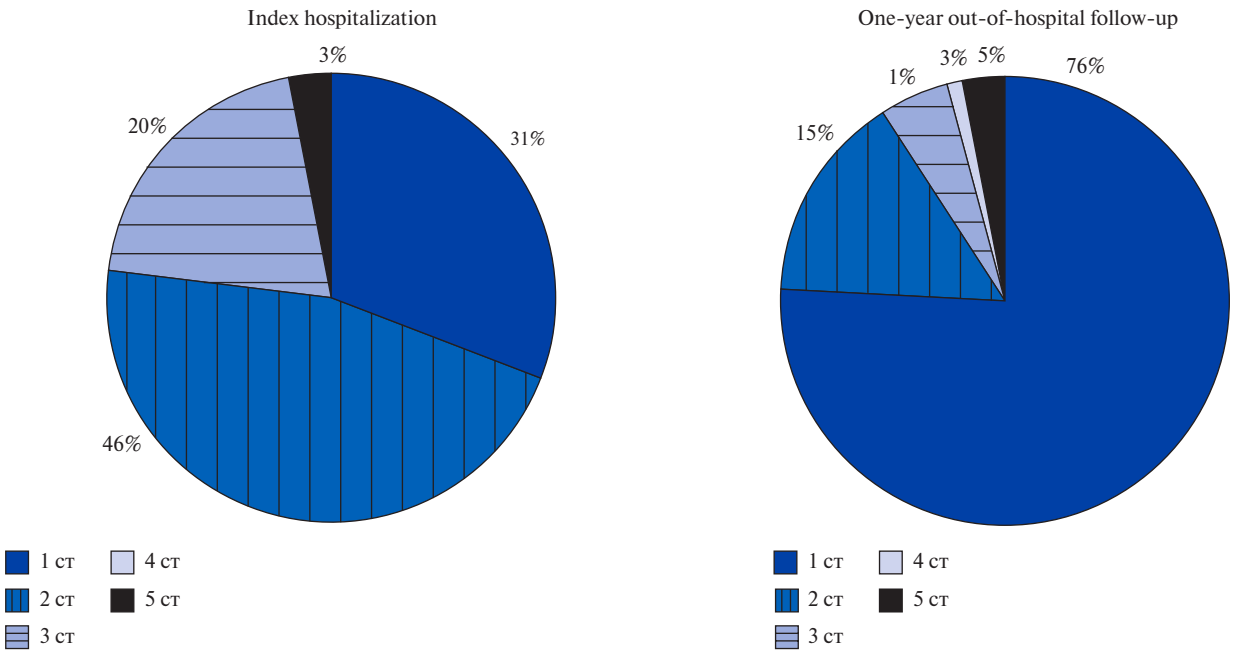


**Fig. 2.** The severity of bleeding during the index hospitalization and one-year out-of-hospital follow-up.

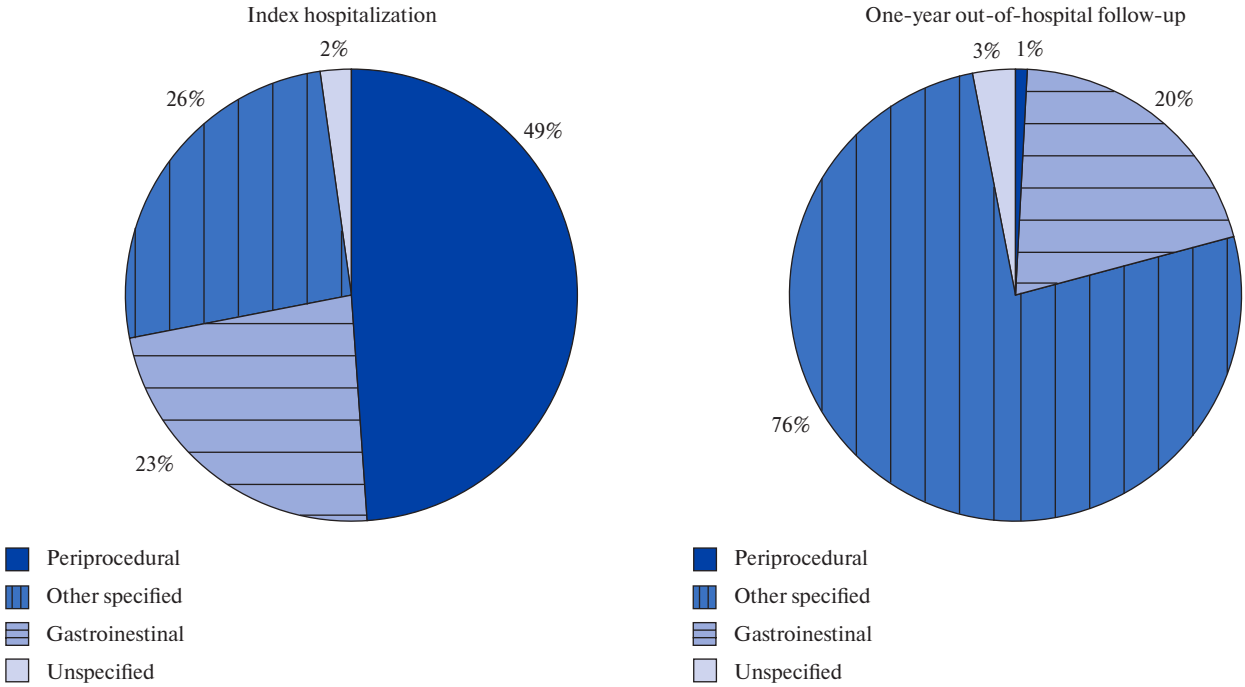


**Fig. 3.** Sources of bleeding during the index hospitalization and one-year out-of-hospital follow-up.

words "acute coronary syndrome", "bleeding", "BARC". The meta-analysis included studies with follow-up periods comparable to the ORACUL study. The meta-analysis of proportions was carried out using the MedCalc statistical software with the Freeman-Tukey's transformation. The heterogeneity of the model was evaluated by the Q and I2 tests.

Logistic regression was used to assess the independence of the effects of clinical factors on the bleeding risk. Parameters that demonstrated statistical significance in a univariate model were included in a multivariate analysis. The coefficients for forecast formula were calculated by linear regression analysis. Internal validation was performed using

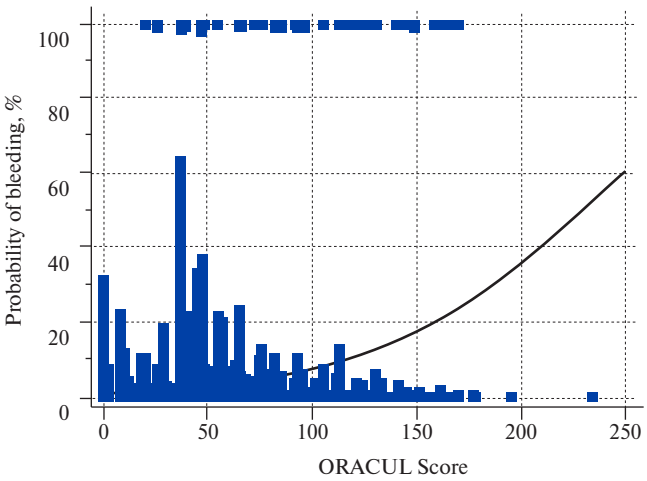


**Fig. 4.** Distribution of ORACUL whole-numbered risk score and the probability of clinically significant bleeding (type 2-5 by BARC classification) within 1 year after ACS.

the bootstrap method. Classification and assessment of the goodness of fit was carried out by Hosmer-Lemeshow test. Classification was considered adequate when p>0,20.

Analysis of the diagnostic accuracy of the test scale was conducted by constructing receiver operator characteristic curves (ROC-curves) for each diagnostic criterion and finding the area under the curves. Also, for each tested diagnostic criterion, sensitivity and specificity were calculated. Comparison of diagnostic values in different clinical groups was carried out by comparing the areas under the ROC-curves by the Hanley and McNeil test.

This independent, open-label, observational, multicenter study was organized by the Department of Therapy, Cardiology and Functional Diagnostics of the Central State Medical Academy (Moscow,

**Table 3**

**Clinical characteristics of patients with ACS depending on the presence of clinically significant bleeding**

| Parameter | Patients without bleeding or with type 1 bleeding 1 (by BARC classification) (n = 1443) | Patients with type 2-5 bleeding (by BARC) (n = 59) | p |
|---|---|---|---|
| Men/Women (n, %) | 863 (59,7%)/580 (40,1%) | 32 (54,2%)/27 (45,8%) | 0,648 |
| Age, years | 65,6±12,91 | 70,8±12,70 | 0,002 |
| BMI, kg/m$^2$ | 28,3±5,01 | 28,0±4,49 | 0,477 |
| STE-ACS/ NSTE-ACS, (n, %) | 541 (37,4%)/902 (62,6%) | 19 (32,0%)/40 (68,0%) | 0,233 |
| History of CAD, (n, %) | 1075 (74,4%) | 47 (76,7%) | 0,789 |
| History of MI, (n, %) | 441 (31,0%) | 25 (42,4%) | 0,066 |
| History of HTN, (n, %) | 1270 (88,0%) | 50 (84,7%) | 0,239 |
| History of AF, (n, %) | 267 (18,5%) | 16 (37,1%) | 0,102 |
| History of stroke, (n, %) | 160 (10,2%) | 4 (6,9%) | 0,145 |
| HF before current hospitalization, (n, %) | 737 (51,1%) | 32 (54,2%) | 0,666 |
| Class 2-4 by Killip, n (%) | 280 (19,1%) | 17 (28,1%) | 0,050 |
| Peripheral artery disease, (n, %) | 388 (27,0%) | 13(22,0) | 0,671 |
| COPD, (n, %) | 63 (4,4%) | 3 (5,1%) | 0,781 |
| Asthma, (n, %) | 32 (2,2%) | 4 (6,8%) | 0,052 |
| Sleep apnea, (n, %) | 29 (2,0%) | 1 (1,7%) | 0,844 |
| Gastroduodenal ulcer, (n, %) | 202 (14,1%) | 14 (23,7%) | 0,038 |
| History of GIB, (n, %) | 21 (1,5%) | 5 (8,9%) | 0,003 |
| Hepatic disorders, (n, %) | 91 (6,3%) | 4 (6,8%) | 0,792 |
| Thyroid disorders, (n, %) | 168 (11,7) | 10 (16,9%) | 0,482 |
| History of anemia, (n, %) | 119 (8,6%) | 12 (20,7%) | 0,010 |
| History of kidney disease, (n, %) | 556 (38,7%) | 28 (44,1%) | 0,759 |
| History of cancer, (n, %) | 124 (8,6%) | 7 (12,1%) | 0,673 |

| | | | |
|---|---|---|---|
| Alcohol consumption, (n, %) | 651 (45,6%) | 21 (35,6%) | 0,434 |
| Smoking, (n, %) | 390 (27,0%) | 15 (25,4%) | 0,758 |
| History of CVD, (n, %) | 528 (38,9%) | 25 (43,1%) | 0,713 |
| Antithrombotic therapy upon discharge from the hospital | | | |
| No therapy, (n, %) | 6 (0,5%) | 2 (3,7%) | 0,052 |
| ASA or clopidogrel (monotherapy), (n, %) | 87 (6,6%) | 2 (3,7%) | 0,056 |
| ASA+ticagrelor, (n, %) | 563 (43,0%) | 21 (38,9%) | 0,156 |
| ASA+clopidogrel, (n, %) | 543 (41,5%) | 20 (37,0%) | 0,169 |
| Triple ATT, (n,%) | 58 (4,4%) | 5 (9,3%) | 0,008 |
| Antiplatelet agent+anticoagulant, (n, %) | 45 (3,4%) | 4 (7,4%) | 0,003 |
| Anticoagulant, (n,%) | 5 (0,4%) | 0 | 0,237 |
| PCI in index hospitalization, (n, %) | 748 (56,3%) | 42 (75,0%) | 0,006 |
| Laboratory parameters upon admission to the hospital | | | |
| HB, $*10^9$/L | 135,9±19,15 | 125,6±6,82 | 0,001 |
| Hematocrit, % | 40,6±6,36 | 38,2±0,68 | 0,011 |
| Leukocytes, $*10^{12}$/L | 11,0±22,30 | 9,9±3,85 | 0,626 |
| Platelets, $10^3$/μL | 236,5±75,79 | 227,5±82,65 | 0,522 |
| Glucose, mmol/L | 8,32±4,74 | 8,42±3,11 | 0,532 |
| Total cholesterol, mmol/L | 5,63±2,641 | 5,49±1,671 | 0,791 |
| LDL, mmol/L | 3,24±1,122 | 3,21±1,466 | 0,184 |
| HDL, mmol/L | 1,11±0,394 | 1,18±0,431 | 0,669 |
| Triglycerides, mmol/L | 1,74±1,231 | 1,51±1,009 | 0,249 |
| Uric acid, mmol/L | 396,7±279,98 | 489,77±214,547 | 0,083 |
| Creatinine, μmol/L | 98,87±36,435 | 100,11±25,443 | 0,578 |
| CrCL by Cockcroft-Gault equation, ml/min | 78,8±32,76 | 66,4±25,17 | 0,01 |
| GFR by MDRD equation, ml/min/1,73 $m^2$ | 42,07±13,361 | 44,87±11,274 | 0,297 |

**Abbreviations:** BMI — body mass index, STE-ACS — ST segment elevation ACS, NSTE-ACS — non-ST segment elevation ACS, CAD — coronary artery disease, MI — myocardial infarction, HTN — hypertension, HF — heart failure, COPD — chronic obstructive pulmonary disease, GIB — gastrointestinal bleeding, CVD — cardiovascular disease, ASA — acetylsalicylic acid, ATT — antithrombotic therapy, PCI — percutaneous coronary intervention, Hb — hemoglobin, LDL — low density lipoproteins, HDL — high density lipoproteins, CrCl — creatinine clearance, GFR — glomerular filtration rate.

Russia). The authors do not declare conflicts of interest.

## Results

During the follow-up period, bleeding was noted in only 164 out of 1502 patients (10,9%), during the index hospitalization — in 39 (2,6%), within year after the index hospitalization — in 126 (8,4%); repeated bleedings on several visits was recorded in 19 (1,2%) patients. The incidence of major bleeding (types 3-5 by BARC) during hospitalization was 0,5%, significant bleeding — 1,7% (types 2-5 by BARC). For bleeding that developed after discharge from the hospital, the incidence was 0,8%, for significant — 2,4%. The severity and sources of bleeding are described in Table 2.

Fig. 1 shows the results of meta-analysis of bleeding incidence in ACS patients according to studies published in 2015-2018 [7-18]. Meta-analysis contains only those studies where the bleeding severity was assessed according to BARC criteria. The incidence of bleeding in hospitalization and within 1 year after an ACS episode was analyzed. It should be noted that the data are very heteroge-

**Table 4**

**Independent predictors of type 2-5 bleeding by BARC classification**

| Factors | Type 2-5 bleeding by BARC classification | | | |
|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | |
| | OR (CI 95%) | p | OR (CI 95%) | p |
| Age, quartiles | 2,58 [1,59-4,18] | 0,001 | 2,66 [1,19-2,31] | 0,003 |
| Class 2-4 by Killip upon admission | 2,16 [1,51-3,11] | 0,017 | 2,01 [1,17-2,96] | 0,033 |
| Gastroduodenal ulcer | 1,91 [1,03-3,55] | 0,04 | 5,00 [1,154-1,71] | 0,031 |
| History of GIB | 6,23 [2,26-17,19] | 0,001 | 0,95 [0,68-1,32] | 0,799 |
| History of anemia | 2,55 [1,32-4,93] | 0,005 | 1,13 [0,63-1,68] | 0,754 |
| Anticoagulants as part of a triple or dual ATT | 2,24 [1,07-4,72] | 0,032 | 1,74 [1,01-2,47] | 0,047 |
| PCI in index hospitalization | 2,31 [1,25-4,28] | 0,007 | 3,03 [1,44-6,37] | 0,003 |
| Hb, quartiles | 2,29 [1,59-3,33] | 0,0001 | 1,97 [1,06-2,87] | 0,045 |
| Hematocrit, quartiles | 1,94 [1,08-2,76] | 0,03 | 0,99 [0,67-1,38] | 0,899 |
| CrCL by Cockcroft-Gault equation, ml/min, quartiles | 1,60 [1,13-2,28] | 0,008 | 2,12 [1,43-2,86] | 0,02 |

**Abbreviations:** GIB — gastrointestinal bleeding, ATT — antithrombotic therapy, PCI — percutaneous coronary intervention, Hb — hemoglobin, CrCl — creatinine clearance.

neous both for the in- and out-of-hospital bleeding (Q-test 319,62 and 820,53, respectively). Funnel analysis for in-hospital bleeding incidence shows symmetrical distribution, and for out-of-hospital bleeding, asymmetrical distribution, which indicates a greater variety of influencing factors. In both cases, the ORACUL study data were within the 95% confidence interval.

During the index hospitalization, bleeding associated with coronary angiography (CAG) and revascularization were the most frequent — 49%; gastrointestinal bleeding (GIB) were in the second place — 23%. One of the bleeding was fatal (aortic dissection) (Fig. 2). After discharge from the hospital, nasal, gingival, urological and some other hemorrhages were most common (76%); GIB were in the second place (20%). Periprocedural (1%) and unspecified (3%) bleeding were rare (Fig. 3). During the index hospitalization, the severity of bleeding corresponded to type 2 (40%) and type 3 (22%) by BARC classification; there was 1 case of fatal bleeding (3%) (type 5). After discharge from the hospital, nuisance bleeding was more often observed (type 1) (76%). Two cases of bleeding associated with coronary artery bypass grafting (CABG) (type 4) and 3 cases of fatal bleeding (type 5) were noted. In general. type 2-5 bleeding (minor, major, CABG-related and fatal) was noted in 64 patients (37,6%).

Given the absolute number of bleeding and the significance of types 2-5 bleeding, they were combined to calculate the risk. It was revealed that the development of type 2-5 bleeding is associated with a gastric and duodenal ulcers, a history of GIB, kidney diseases and creatinine clearance decrease, a history of anemia and levels of hemoglobin and hematocrit upon admission. It was also associated with age, anticoagulants as part of a triple or dual ATT, PCI during index hospitalization and class 2-4 by Killip upon admission (Table 3).

According to the regression analysis, the following factors were independently associated with bleeding: age, hemoglobin and creatinine clearance decrease, PCI in index hospitalization, the use of oral anticoagulants, class 2-4 by Killip, and a history of peptic ulcer disease (Table 4). These factors were included in the ORACUL risk assessment model. For computational convenience, the coefficients obtained in the regression analysis were converted to whole numbers (points). For each continuous variable, cut-off points were created at which the ratio between the variable and the bleeding risk became flat and clinically significant (Table 5). The point total for each patient was compared with the risk of bleeding (Fig. 4). With the internal validation, the following classification intervals were obtained: with a total of up to 67 points, the bleeding risk is low (<1,5%), 68-107 points — moderate (2,8%), 108-133 points — high (5,1%), over 134 points — very high — 11,7% (Table 6). Moreover, in the lower classification

**Table 5**

**ORACUL score**

| Parameters | |
|---|---|
| Age up to 55 years old<br>56-65 years old<br>66-75 years old<br>Over 75 years old | 0 points<br>8 points<br>16 points<br>24 балла |
| Hemoglobin upon admission >125 g/L<br>100-125 g/L<br><100 g/L | 0 points<br>48 points<br>96 points |
| Killip class upon admission | |
| Class 1 | 0 points |
| Class 2-4 | 17 points |
| Creatinine clearance<br>≥90 ml/min<br>60-89 ml/min<br><60 ml/min | <br>0 points<br>6 points<br>12 points |
| History of gastroduodenal ulcer | 20 points |
| Anticoagulant+ antiplatelet agents after ACS (dual or triple therapy) | 36 points |
| PCI in index hospitalization | 38 points |

**Abbreviations:** ACS — acute coronary syndrome, PCI — percutaneous coronary intervention.

**Table 6**

**Internal validation of ORACUL score**

| Internal | % adverse outcome | The ratio of the probability to the expected | 95% CI |
|---|---|---|---|
| 0-67 | 1,5% | 0,555 | 0,388-0,792 |
| 68-107 | 2,8% | 1,269 | 0,783-2,054 |
| 108-133 | 5,1% | 1,987 | 1,021-3,868 |
| 134-250 | 11,7% | 6,831 | 3,562-13,099 |

interval, the risk of bleeding was lower than expected, and in the intervals of 68 points or more — higher than expected.

The risk classification by the ordered score was adequate — p=0,576 by the Hosmer-Lemeshev test, and the prognostic value was high (ROC-curve — 0,762) (Fig. 5). The sensitivity of the model was 62%, specificity — 78%.

## Discussion

Bleeding events in patients with ACS can be one of the most important unfavorable prognostic factors. For the first time, the effect of bleeding on the prognosis of ACS patients was shown in meta-analysis with 24 thousand patients of 3 studies — GUSTO

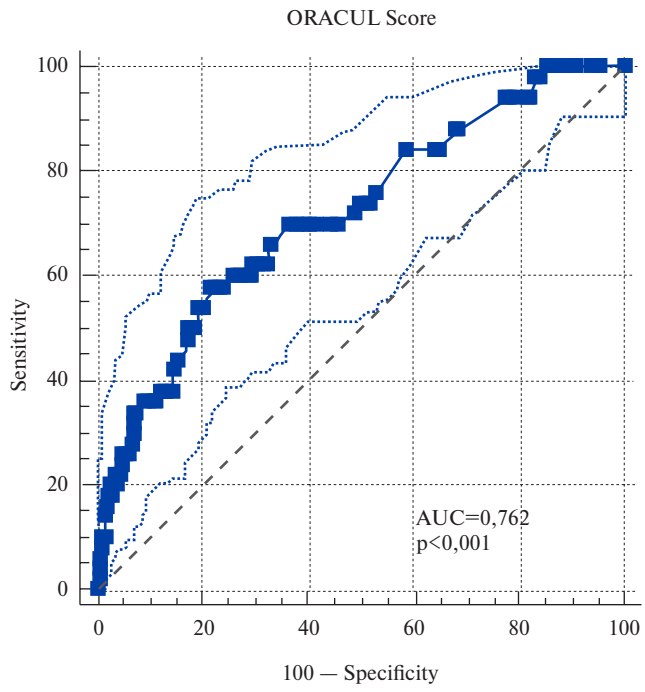


**Fig. 5.** ROC-curve for the ORACUL score.

IIb, PURSUIT and PARAGON B. Meta-analysis showed that patients who received a blood transfusion during hospitalization due to ACS have a significantly higher mortality rate and recurrent myocardial infarction (MI) during the first 30 days after ACS [19]. In the OASIS-5 study, fondaparinux was significantly safer than enoxaparin with similar efficacy during treatment. During follow-up after treatment, ischemic events were also significantly less common in the fondaparinux group, which suggests that every sixth death recorded in ACS patients in the first 30 days from the destabilization occurred in patients with bleeding during hospitalization [20]. A subanalysis of the PLATO study also showed that the increased risk of adverse outcome after early spontaneous ischemic events and after episodes of major bleeding is comparable. Moreover, bleeding often precede recurrent ischemic events [21]. A similar correlation of hemorrhagic and ischemic events was revealed in the Swiss cohort of patients with ACS, including 1901 patients. The risk assessment scale, which includes only 3 parameters (age, ejection fraction and creatinine level), made it possible to predict the risk of coronary events, death and strokes. At the same time, the severity of bleeding, evaluated by the TIMI and GUSTO scales, correlated with an increase in the number of points of the coronary risk [22]. ACS patients commonly (10-40% of cases) are diagnosed with anemia, which can also be a symptom of

severe concomitant diseases. In some patients, a hemoglobin decrease occurs during treatment in a hospital and is associated with active antithrombotic therapy and bleeding. As a rule, in-hospital bleeding and a hemoglobin decrease correlate with an unfavorable prognosis of coronary artery disease and an increased risk of thrombotic complications [23]. Such data emphasize the need for prediction and possible prevention of bleeding in ACS patients, as well as maintaining a balance of thrombotic and bleeding risks during therapy.

When using the BARC bleeding classification [6], it was shown that the increased risk of recurrent ischemic events in ACS patients is typical for type 2-5 bleeding; type 1 (nuisance) bleeding does not significantly affect the risk of adverse outcomes [24]. Prognostic value of class 3b hemorrhages was comparable with repeated MI. The mortality rate after recurrent MI was significantly lower than after class 3c bleeding [25].

In our paper, the incidence of significant bleeding was lower than in most previously published studies. Our meta-analysis showed a high heterogeneity of data on the bleeding incidence, which may be associated with ATT. At the same time, in-hospital bleeding during index hospitalization demonstrates a greater homogeneity of data. The large scatter of data requires additional analysis of methods for assessing the bleeding severity, and also indicates the need to improve forecast models.

In the BleeMACS register, the incidence of major bleeding (3-5 types by BARC) in the first year after PCI was 3,2% per year (in our study — 2.3%). It is worth noting that these patients are close to those included in our study by their main clinical characteristics. Also, the factors used in BleeMACS bleeding risk score was close to those from ORACUL study [26]. Both models include factors such as age, creatinine and hemoglobin levels. In our risk assessment model, a history of peptic ulcer was more significant factor than a bleeding history (as in BleeMACS). The history of cancer did not significantly affect the prognosis. It should be noted that factors such as age, hemoglobin level (or anemia history), decreased renal function are included in most risk assessment models for bleeding [27, 28]. A decrease in creatinine clearance below 60 ml/min is used as an independent factor in the PARIS score [29]. In our register, glomerular filtration rate (GFR) was not used. The American register of ACS patients, including 1699 patients from 3 centers, compared the prognostic value of GFR using the MDRD and CKD-EPI formulas and creatinine clearance using Cockcroft-Gault formula regarding the risk of hemorrhagic and thrombotic events. It showed that creatinine clearance had higher diagnostic value in assessing the risk of coronary events and overall mortality compared with MDRD GFR and risk of bleeding compared with CKD-EPI GFR [30].

In the PARIS score, one of the prognostic factors is the anticoagulant as a part of a triple ATT; in our risk score, any use of anticoagulants was a predictor of a high bleeding risk.

Heart failure upon admission to the hospital was another independent risk factor for bleeding in our study. Heart failure is also used in the ACTION and CRUSADE scores [31, 32]. In one study, a reduced ejection fraction was used as an independent risk factor for bleeding [33].

The management of patients was also significant in our study — patients after PCI had a 3 times higher risk of bleeding. This is consistent with the ACCOAST study, where PCI increased the risk of bleeding by 2,2 times [33].

Thus, the ORACUL score showed high prognostic value for assessing the risk of all significant bleeding within 1 year after ACS. The score is easy to use and predicts bleeding in actual clinical practice. These factors allow for the implementation of the score in practice.

**Conflicts of Interest:** nothing to declare.

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# Epicardial fat thickness and biomarkers of inflammation in patients with stable coronary artery disease: correlation with the severity of coronary atherosclerosis

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**Aim.** To study the relationship between the epicardial fat thickness (EFT), biomarkers of inflammation and metabolic dysfunction in patients with coronary artery disease (CAD) and various severity of coronary atherosclerosis.

**Material and methods.** The study consisted of 89 patients (47 men and 42 women) with stable CAD at the age of 62,2±6,5 years, who assessed the presence and severity of coronary atherosclerosis according to angiography with the calculation of the Gensini Score (GS). We conducted an ultrasonic evaluation of the EFT. We determined the content of glucose, lipid fractions, apoproteins, pro-inflammatory cytokines and adipokines, C-reactive protein by a highly sensitive method (hsCRP).

**Results.** In the total sample of patients, the median GS index was 13,5 (3,5; 43) points, the median EFT was 4,93 (3,95; 6,0) mm, the median hsCRP was 2,1 (1,02; 3,65) mg/l. There were no correlation relationships between the GS index and the body mass index, waist circumference, EFT, hsCRP, lipid and carbohydrate metabolism in the general group of patients. In the course of linear regression analysis, an independent contribution of hsCRP >2,1 mg/l to the formation of the first two tertiles of a sample of GS values was established (0⩽ GS ⩽28, paired linear regression hsCRP at GS β=0,55, p=0,0221), whereas in patients with GS values from the third tertile (GS >28 points), the growth of this parameter had an independent association with an increase in the EFT (estimation of the coefficient of paired linear regression of the EFT on GS β=0,56, p=0,0015). The range of hsCRP changes did not affect the value of the β coefficient in paired linear regression models in patients with GS >28 points (n=29) and in the subgroup of patients with GS >28 and hsCRP >2,1 mg/l (n=18).

**Conclusion.** The absence of an independent association between EFT and minor or moderate severity of atherosclerotic lesions of the coronary arteries (for GS ⩽28 points) in patients with CAD, while an independent marker of GS index increase is higher than 2,1 mg/l. An independent contribution to the formation of a severe coronary atherosclerosis (with a GS value of >28 points) is equally made by thickening of EFT, and a moderately elevated level of hsCRP.

**Key words:** epicardial fat thickness, biomarkers of inflammation, coronary atherosclerosis, Gensini Score. Conflicts of interest: nothing to declare.

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Epicardial adipose tissue (EAT) is a metabolically active ectopic depot of visceral and perivascular fat cells not separated by fascia from the myocardium and coronary arteries (CA). Under disorders, it can activate local and paracrine secretion of various pro-atherogenic mediators [1]. Although many studies have shown that epicardial adiposity can be considered as a visual surrogate marker for CA and its severity [2-4], the pathophysiological mechanisms that mediate the relationship between epicardial adiposity and atherogenesis still need to be clarified. So far, the independent association between EAT thickness and CA have not been established; its diagnostic value as a tool for individual risk stratification in patients with coronary artery disease (CAD) also requires clarification. Based on the inflammatory hypothesis of atherosclerosis, assessing the biomarkers of chronic subclinical inflammation is widely used to clarify cardiovascular risk in CAD patients. Nevertheless, the data on the association of high-sensitivity C-reactive protein (hsCRP) increase with CAD are very contradictory. So, some authors suggest their close relationship [5], while others deny this [6, 7]. Since the EAT has a proven independent association with hsCRP increase [8], it is possible that the severity of EAT accumulation and its dysfunction can specify associations between the hsCRP content and CA. In the modern literature there is no comprehensive information about the nature of the relationship between EAT, the activity of chronic subclinical inflammation and the CA severity. Moreover, the characteristics of this relationship at different stages of atherogenesis are not clear. The aim of this paper was to study the relationships of EAT thickness, inflammatory biomarkers, and severity of metabolic dysfunction with CA of different extent using the Gensini Score (GS) in patients with CAD.

## Material and methods

The study was conducted in accordance with Good Clinical Practice guidelines and the principles of Declaration of Helsinki; the study protocol was approved by local independent ethics committee. The study included men and women aged 40 to 70 years with established stable CAD who underwent coronary angiography. All patients completed the informed consent.

Exclusion criteria were acute complication of atherosclerosis, less than 6 months ago and any inflammatory disease; diabetes with inadequate glycemic control and HbA1c>10% or glycemia during the day >11 mmol/L; chronic kidney disease above G3b, left ventricular ejection fraction <40%; oncological, hematological and immune diseases.

Table 1 presents the clinical characteristics of the included patients. The study consisted of 89 men and women with established stable CAD at the age of 62,2±6,5 years. About half of the patients had type 2 diabetes (T2D) and the same proportion was smokers. Metabolic disorders that met the criteria of metabolic syndrome [9] were determined in 72% of patients. Hemodynamically significant stenosis of at least one of the main coronary arteries was established in 68,6% of patients; coronary microvascular stenosis was observed in 23,6% of patients. In other cases, changes in coronary arteries were considered non-stenotic.

All patients underwent selective coronary angiography using the Cardio-scop-V apparatus and Digitron-3NAC software (Siemens (Germany)). The procedure was conducted by specialists of Endovascular Surgery Department headed by Ph.D. A. E. Baev. The severity of coronary artery injury was assessed by GS.

The EAT thickness was determined by parasternal long-axis echocardiographic left ventricle (LV) images obtained at end-systole [10]. The measurements were carried out over 3 cardiac cycles; the average of 3 serial measurement results was taken as the EAT value.

Body mass index (BMI) was used to assess the general obesity, waist circumference (WC) — abdominal obesity.

By the method of enzyme immunoassay, the content of hsCRP (Biomerica, Germany), insulin (Accu-Bind, USA), interleukin (IL) -6 (Vector-BEST, Russia), tumor necrosis factor (TNF)-α (Affymetrix, eBioscience, USA), resistin (Mediagnost, Germany), leptin (Mediagnost, Germany), adiponectin (Assaypro, USA), apolipoprotein A1 (DiaSys, Germany) were determined in the blood serum. The blood glucose levels were determined by the glucose oxidase method; HbA1c proportion was determined by immunoturbidimetric assay (DiaSys, Germany). Blood lipids (total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) (sets by ZAO Diakon-DS, Russia) were studied.

**Statistical analysis.** Statistical analysis was carried out using the Statistica 10.0 software. The median and interquartile range between the 25th and 75th percentiles were used to describe distribution features. Differences in quantitative characters in independent groups of patients were identified using the Mann-Whitney and the Kruskal-Wallis tests. When studying the relationship of the GS with various bio-

**Table 1**

**Clinical characteristics of the included patients (n=89)**

| Parameter | |
|---|---|
| Gender (men/women) | 47/42 |
| Age, years | 60,2±6,5 |
| The proportion of patients with a history of myocardial infarction, n (%) | 32 (36%) |
| Duration of coronary artery disease, years* | 2 (1; 5) |
| The proportion of patients with type 2 diabetes, n (%) | 37 (41,6%) |
| Duration of diabetes, years* | 5,5 (2; 12) |
| The proportion of patients with hypertension, n (%) | 18 (20,2) |
| Duration of arterial hypertension, years* | 10 (5; 15) |
| Systolic blood pressure, mm Hg | 127,2±14,1 |
| Diastolic blood pressure, mm Hg | 77,7±8,4 |
| The proportion of smokers, n (%) | 37 (41,6%) |
| Body mass index, kg/m$^2$ | 30,1±4,3 |
| The proportion of patients with overweight, n (%) | 42 (47,2%) |
| The proportion of patients with obesity, n (%) | 42 (47,2%) |
| Waist circumference, cm | 102,5±13,9 |
| Thigh circumference, cm | 104,7±8,1 |
| Waist circumference / thigh circumference | 0,96±0,1 |
| LDL-C, mmol/L | 2,92±1,28 |
| Statin therapy, n (%) | 63 (70,8%) |
| $Hb_{A1c}$ (patients with diabetes),% | 7,74±1,44 |
| Antihypertensive therapy, n (%) | |
| — RAAS inhibitors | 68 (76,4%) |
| — β-blockers | 64 (71,9%) |
| — calcium channel antagonists | 26 (29,2%) |
| — thiazide diuretics | 22 (24,7%) |
| — β-blockers and diuretics | 17 (19,1%) |

**Note:** * — data are presented as Me (($Q_{25\%}$; $Q_{75\%}$)).
**Abbreviations:** CAD — coronary artery disease, RAAS — renin-angiotensin-aldosterone system, LDL-C — low density lipoprotein cholesterol.

markers, the Spearman's rank correlation coefficient (Rs) was determined. In cases where significant correlation was identified, linear regression models were constructed. The relationship between the GS and qualitative characters was assessed using four-field contingency tables. The results of statistical analysis were considered statistically significant at p<0,05.

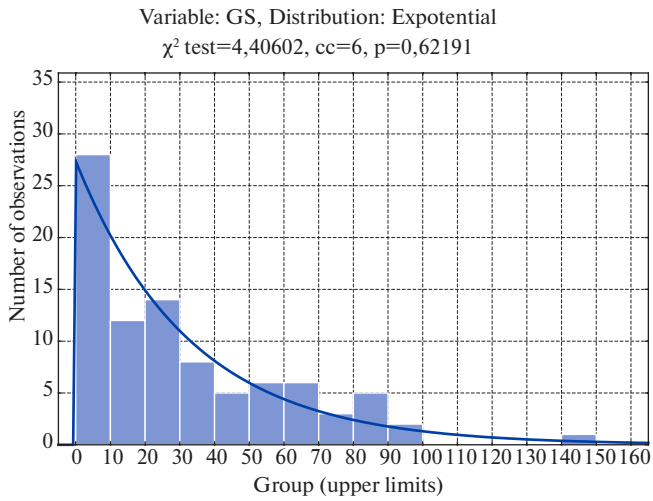


**Fig. 1.** The histogram of distribution of GS sample values.

## Results and discussion

The histogram of distribution of GS sample values is shown in Fig. 1. As seen, the sampling of the GS values has a wide scatter: from 0 (in 21 patients) to 144. Fig. 2 and 3 show scatter plots characterizing the correlation between the GS and EAT thickness and hsCRP values.

In the general group of patients, the GS median was 13,5 (3,5; 43), the EAT thickness median — 4,93 (3,95; 6,0) mm, the hsCRP median — 2,1 (1,02; 3,65) mg/L. There were no correlation between the GS in its entire range and age, gender, BMI, WC, EAT thickness, hsCRP, TC, LDL-C, TG and carbohydrate metabolism in the general group of patients, but associations of the GS with IL-6 levels ($R_s$=0,33) and HDL-C ($R_s$=-0,25) were established (Table 2). Our data are consistent with the study by Caselli C, et al. (2015), which showed that the IL-6 and HDL-C determination allows to predict the presence and severity of CA determined by computed tomography [11]. At the same time, the values of EAT thickness in our sample did not correlate with GS, inflammatory biomarkers, parameters of lipid and carbohydrate metabolism, and showed linear associations with BMI ($R_s$=0,47), abdominal obesity ($R_s$=0,42), WC ($R_s$=0,36) and leptin ($R_s$=0,36). It should be noted that a EAT thickness ⩾5 mm was determined in 21 patients (24%) with general and abdominal obesity (10 men and 11 women) without established CA or with insignificant coronary artery changes.

Since the sample values of the GS has a "zero-inflated" distribution, all patients were divided into three subgroups by GS tertiles: 0-5 (n=30), 6-28 (n=30) and more than 28 (n=29). The patients of the

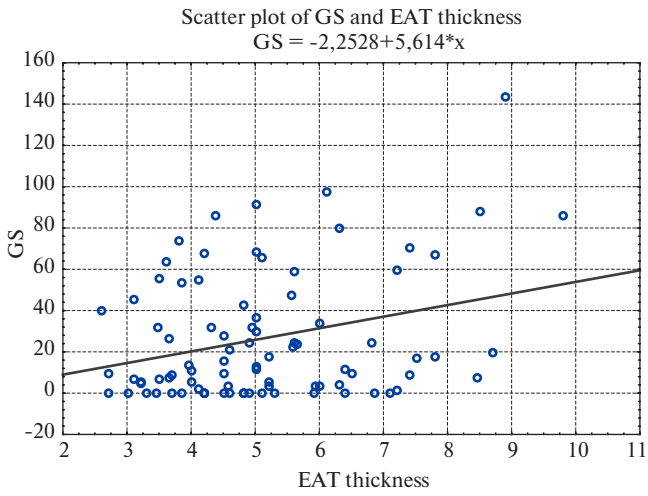


**Fig. 2.** Scatter plot of GS and EAT thickness.

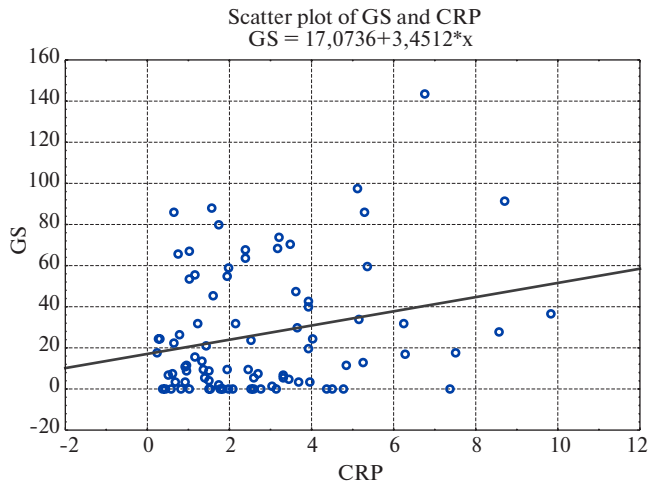


**Fig. 3.** Scatter plot of GS and CRP.

**Table 2**

**Correlations between the studied parameters in CAD patients**

| Parameters | GS | BMI | WC | EAT thickness | HDL-C | TG | hsCRP | IL-6 | Leptin | Adiponectin |
|---|---|---|---|---|---|---|---|---|---|---|
| GS | | | | | -0,25 | | | 0,33 | | |
| BMI | | | | 0,47 | | 0,25 | 0,29 | | 0,60 | |
| WC | | | | 0,36 | | | 0,25 | | | -0,26 |
| EAT thickness | | 0,47 | 0,36 | | | | | | 0,36 | |
| HDL-C | -0,25 | | | | | -0,28 | | -0,23 | | 0,39 |
| TG | | 0,25 | | | -0,28 | | 0,23 | | | -0,23 |
| hsCRP | | 0,29 | 0,25 | | | 0,23 | | 0,40 | 0,24 | 0,40 |
| IL-6 | 0,33 | | | | -0,23 | | 0,40 | | | |
| Leptin | | 0,60 | | 0,36 | | | 0,24 | | | 0,27 |
| Adiponectin | | | -0,26 | | 0,39 | -0,23 | 0,40 | | 0,27 | |

**Note:** all noted correlations are significant, $p<0,05$.

**Abbreviations**: CAD — coronary artery disease, BMI — body mass index, WC — waist circumference, TG — triglycerides, EAT — epicardial adipose tissue thickness, HDL-C — high density lipoprotein cholesterol, GS — Gensini Score, hsCRP — high-sensitivity C-reactive protein, IL-6 — interleukin-6.

first two tertiles were combined into group 1 (GS⩽28, n=60), and the studied parameters were analyzed in comparison with the patients of group 2 from the GS third tertile (GS>28, n=29) (Table 3).

As seen, there were no significant intergroup differences by gender, age, blood pressure (BM), BMI, EAT thickness, levels of LDL-C, TG, $HbA_{1c}$ and adipokines, as well as the proportion of patients with T2D and taking lipid-lowering therap. Among patients of group 2, the proportion of smokers and the atherogenicity index were higher and the apoA1 level was lower, which reflects a characteristic decrease in the HDL-C anti-atherogenic potential in patients with severe CA. In addition, patients of group 2 were characterized by a higher hsCRP levels in comparison with group 1, where hsCRP <1 mg/L were significantly more common (Table 4).

Dysfunctional EAT is an atherogenic trigger which can secrete both local and systemic mediators of atherogenesis, which contributes to the systemic formation of free radicals and the development of chronic subclinical inflammation [1]. Therefore, it was important to establish whether a quantitative assessment of EAT thickness can independently predict the presence and severity of CA in patients with established CAD.

**Table 3**

**Clinical characteristics, thickness of epicardial adipose tissue and laboratory parameters in patients with coronary artery disease depending on the presence and severity of coronary atherosclerosis, assessed by Gensini Score (Me ($Q_{25\%}$; $Q_{75\%}$))**

| | Group 1 (n=60) GS 0-28 | Group 2 (n=29) GS >28 баллов | p |
|---|---|---|---|
| GS | 5,25 (0; 12,5) | 60 (43; 74) | 0,000 |
| Men/Women | 29 (48,3%)/31 (51,7%) | 18 (62,1%)/11 (37,9%) | |
| Age, years | 61,5 (56; 66,5) | 60 (55; 65) | |
| Smoking, n (%) | 20 (33,3%) | 17 (58,6%) | 0,03 |
| Patients with T2D, n (%) | 18 (30) | 10 (34,5) | |
| Lipid-lowering therapy, n (%) | 41 (68,3%) | 22 (75,9%) | |
| BMI, kg/m$^2$ | 29,6 (27,7; 31,1) | 30 ( 26,3; 33,3) | |
| WC, cm | 100 (94; 105) | 102,5 (90; 108) | |
| EAT thickness, mm | 4,85 (3,90; 5,97) | 5,0 (4,1; 6,1) | |
| hsCRP, mg/L | 1,87 (0,94; 3,36) | 3,14 (1,6; 5,12) | 0,04 |
| IL-6, pg/ml | 1,36 (1,01; 1,85) | 2,23 (1,48; 3,31) | 0,003 |
| TNF-α, pg/ml | 0,50 (0,48; 0,91) | 0,42 (0,30; 0,70) | |
| LDL-C, mmol/L | 2,50 (1,86; 3,63) | 2,72 (2,29; 3,80) | |
| HDL-C, mmol/L | 1,08 (0,96; 1,32) | 1,00 (0,83; 1,12) | 0,04 |
| Triglycerides, mmol/L | 1,43(1,13; 2,06) | 1,57 (1,13; 2,01) | |
| Atherogenic Index | 2,96 (2,23; 4,49) | 3,49 (2,80; 4,95) | |
| ApoA1, mg/dl | 151,6 (133,0; 170,2) | 128,0 (106,8; 156,8) | 0,005 |
| $Hb_{A1c}$,% | 6,34 ( 5,63; 7,20) | 6,01(5,40; 6,90) | |
| Leptin, ng/ml | 18,3 (7,7; 32,8) | 15,2 (6,9; 26,4) | |
| Resistin, ng/ml | 4,51 (3,48; 5,11) | 4,75 (3,89; 5,62) | |
| Adiponectin, ng / ml | 9,23 (6,20; 13,25) | 7,59 (5,21; 10,26) | |

**Abbreviations:** CAD — coronary artery disease, BMI — body mass index, WC — waist circumference, T2D — type 2 diabetes, HDL-C — high density lipoprotein cholesterol, HDL-C — low density lipoprotein cholesterol, GS — Gensini Score, hsCRP — high-sensitivity C-reactive protein, IL-6 — interleukin-6, TNF-α — tumor necrosis factor α.

**Table 4**

**Distribution of patients by hsCRP levels depending on the range of GS values**

| GS | hsCRP <1 mg/L, n (%) | hsCRP 1-3 mg/L, n (%) | hs CRP ≥3 mg/L, n (%) |
|---|---|---|---|
| Group 1: 0-28 | 16 (83,1%) | 24 (58,6%) | 20 (48,3%) |
| Group 2: >28 | 2 (16,9%)* | 12 (41,4%) | 15 (51,7%) |

**Note:** * — differences between gr. 1 and column 2 are statistically significant (p<0,0001).
**Abbreviations:** GS — Gensini Score, hsCRP — high-sensitivity C-reactive protein.

There were no significant correlations between the GS and parameters of general and abdominal obesity, EAT thickness, inflammatory biomarkers and metabolic parameters in patients without CA or mild and moderate CA (group 1, GS ⩽28, n=60). At the same time, after applying the group limiting on the hsCRP level more than the median (>2,1 mg/L), according to the data of linear regression analysis, an independent contribution of hsCRP >2,1 mg/L to the formation of low GS was

**Table 5**

**Model of dual linear regression of hsCRP on GS in patients with GS ⩽28 and hsCRP >2,1 mg/L (n=17)**

| | Beta coefficient* | Standard error of beta* | p |
|---|---|---|---|
| GS | 0,55 | 0,22 | 0,0221 |

**Note:** * — differences between groups 1 and 2 are statistically significant (p<0,0001).
**Abbreviations:** GS — Gensini Score, hsCRP — high-sensitivity C-reactive protein.

**Table 6**

**Model of dual linear regression of the EAT thickness on GS in patients with GS >28 (n=29)**

| | Beta coefficient* | Standard error of beta* | p |
|---|---|---|---|
| EAT thickness | 0,56 | 0,16 | 0,0015 |

**Note:** * — differences between groups 1 and 2 are statistically significant (p<0,0001). Concordance rate $R^2$=0,52.
**Abbreviations:** GS — Gensini Score, hsCRP — high-sensitivity C-reactive protein.

determined. This reflects initial stages of atherogenesis (Table 5).

Linear regression analysis in patients with severe CA (group 2, GS >28) showed an increase of GS and EAT thickness (Table 6). These findings did not depend on the range of hsCRP changes, since the beta coefficient in the dual linear regression model in group 2 practically did not differ from the subgroup of patients having hsCRP >2,1 mg/L (beta*=0,555, p=0,0178).

The results show that there is no direct linear relationship between EAT thickness and the GS, reflecting mild and moderate CA, and its independent determinant is the hsCRP levels more than 2,1 mg/L. At the same time, an independent association between the EAT thickness and the GS is determined only in patients with severe CA (GS >28), and this is not clearly dependent on the range of hsCRP changes. Although a number of cross-sectional and case-control studies have shown the association between increased hsCRP levels and CA severity [5]; some other studies have denied this association [6-7]. Our results suggest that hsCRP levels more than 2,1 mg/L at the initial stages can have an important pathogenetic value, regardless on epicardial adiposity. At the same time, in advanced stages of CA, its severity is equally specified by excessive EAT accumulation and hsCRP increase. It cannot be ruled out that it is the phase nature of the interaction of EAT with inflammatory biomarkers at different stages of atherogenesis that may be the reason for the previously obtained contradictory results [3, 5-7, 12].

It should be noted that in our study, groups of patients with CA of various severity showed no differences in EAT thickness. This does not preclude the possibility that patients with GS ⩽28 may have factors that can "smooth" the atherogenic potential of the EAT depot. In particular, in the group of patients with the GS⩽28, there was a higher levels of HDL-C and ApoA1, lower hsCRP level, while in the general sample, negative association between HDL-C and GS was determined. The results of a study by Chechi K, et al. (2013) allow interpreting these results in relation to their association with the EAT depot activity [13]. Thus, the authors revealed a higher expression of the marker of brown adipose tissue thermogenin (UCP-1) in the epicardial fat depot than in the mediastinal and subcutaneous fat depots. UCP-1 is involved in the thermogenesis, and authors established a direct association between the UCP-1 gene expression and HDL-C levels, which indicates the protective effects of EAT [13]. Our data on the absence in the general group of an independent association of EAT thickness with the CA severity of may be associated with a high proportion of women in the study. In women, the role of epicardial fat depot as an atherogenic factor may be less significant than in men [14]. This is due to the cardioprotective effects of higher aromatase activity of subcutaneous fat [15].

The limitations of our study are: cross-sectional design; the small sample, which does not allow us to establish potential gender differences in the relationship between the CA severity and the EAT accumula-

tion and features of subclinical inflammation; some conventionality for dividing the GS range; no statin therapy at the time of the study in 29,2% patients.

Thus, the results of our study indicate the absence of independent association between EAT thickness and mild or moderate CA (GS⩽28) in patients with established CAD, while an independent marker of an GS increase in such patients is the hsCRP >2,1 mg/L. The thickening of EAT and the hsCRP increase is independently associated with severe CA (GS>28), equally. The obtained results suggest that the phenotypic and functional properties of EAT can significantly change during atherogenesis. In further papers, correlations of the cellular and molecular properties of EAT with its quantitative assessment should be studied.

**Conflicts of Interest:** nothing to declare.

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# Model for calculating the risk of venous thrombosis

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**Aim.** To develop a model for calculating the risk of venous thrombosis, taking into account the presence of known risk factors, comorbidity and congenital thrombophilia.

**Material and methods.** During the study (2015 to 2017), 79 patients with venous thrombosis were examined (36 men and 43 women, mean age — 56,76±15,570). The control group consisted of 83 patients and healthy volunteers without thrombosis at the moment and in history (35 men and 48 women, average age — 43,95±18,136). All individuals included in the study were analyzed for the presence of G1691A mutations in the factor V gene, G20210A in the prothrombin gene, C677T polymorphism in the 5,10-methylenetetrahydrofolate reductase gene, and polymorphism in the SERPINE1 gene of plasminogen activator inhibitor. Real-time polymerase chain reaction was used to identify mutations. To create a risk calculation model, a linear regression analysis was performed.

**Results.** We have developed a model for calculating the risk of venous thrombosis. The resulting formula showed high prognostic accuracy (the area under the ROC curve is 95,9%). For patients who do not have data on the presence of these mutations, a short version of the risk calculation model was developed (the area under the ROC curve is 94,6%).

**Conclusion.** We have developed a risk calculation model taking into account the presence of known risk factors, congenital thrombophilia and comorbidities. Thromboprophylaxis is necessary in >0,45 individual risk, which corresponds to a high risk of developing venous thrombosis. Patients who have not previously been diagnosed with thrombophilia and are in the middle risk group for venous thrombosis, according to a short version of the model, must be screened for congenital thrombophilia to clarify the risk.

**Key words:** congenital thrombophilia, overweight, obesity, venous thrombosis of the lower extremities, pulmonary embolism, risk calculation model.

**Conflicts of Interest:** nothing to declare.

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According to the Global Burden of Disease Study, thromboses cause every fourth death in the world [1]. These data mainly belong in arterial thrombosis, and if venous thrombosis were taken into account, the statistics would be worse. Unfortunately, data on the prevalence and mortality from venous thromboembolism (VTE) are limited and available only in a few large regions. Every year, 10 million new cases of VTE are recorded worldwide. [2]. There are 300-600 thousand VTE-related deaths in the USA per year [3], in Europe — 544 thousand [4]. According to the Russian Phlebological Association, about 80 thousand new cases are annually registered in the Russian Federation [5]. The incidence of VTE has increased significantly over the past decades. That was revealed by population-based cohort study in Olmstead County (USA) [6].

The VTE development is influenced by a large number of factors. There are some predisposing acquired risk factors, such as traumas, surgery, cancer, chemotherapy, hormonal contraceptives and hormone replacement therapy, pregnancy, the postpartum period, immobilization, obesity, old age, etc. [7]. A significant risk factor for thrombosis is congenital thrombophilia [8].

Despite the high prevalence and mortality, VTE is preventable [9]. Proper prevention strategy can significantly reduce the VTE incidence. At the same time, anticoagulant use for prevention will increase the risk of bleeding, especially in elderly patients with severe concomitant pathology and highest risk of thrombosis [10].

We consider that our risk assessment model (RAM) for venous thrombosis can cover the maximum number of factors, and its use in practice will reduce the thrombosis risk and do not significantly increase the bleeding risk.

## Material and methods

The study was conducted from 2015 to 2017. A total of 79 patients with venous thrombosis (36 men and 43 women, mean age 56,76±15,57) who were diagnosed with pulmonary embolism and lower extremity superficial and deep vein thrombosis (44,3%), lower extremity deep vein thrombosis (2,9%) and pulmonary embolism of unknown origin (22,8%) were examined.

The control group consisted of 83 inpatients and healthy volunteers without thrombosis and history of it (35 men and 48 women, mean age — 43,95±18,14).

The inclusion criteria were age over 18 years, the thrombosis, established at the moment or in the history, and completed informed consent. Exclusion criteria were age up to 18 years, pregnancy and first 6 weeks of postpartum period, and cancer.

Diagnosis of thrombosis was carried out in accordance with modern Russian guidelines. During hospitalization, we collected data of medical history and physical, laboratory and instrumental tests. All participants were analyzed for the most common thrombophilia types: G1691A (Factor V Leiden) mutation, prothrombin G20210A mutation, polymorphism (C677T) in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene, plasminogen activator inhibitor-1 (PAI-1) gene (SERPINE1) polymorphism. To detect mutations, real-time PCR was used.

The study was carried out in accordance with the standard of Good Clinical Practice and principles of Declaration of Helsinki. The study protocol was approved by the ethics committees of all participating medical centers. Prior to inclusion, all participants completed written informed consent.

## Results

In a regression analysis, it was found that in order to predict venous thrombosis, it is necessary to assess data such as the patient's age, weight and height, and early deaths in the family history (Table 1). Risk factors for venous thrombosis are major trauma, surgery, and concomitant diseases, such as coronary artery disease (CAD), heart failure (HF) according to NYHA classification, chronic obstructive pulmonary disease (COPD) and exacerbation of inflammatory bowel disease. The duration of asthma, atrial fibrillation (AF) and diabetes are also important. Of congenital thrombophilia, the factor V Leiden and prothrombin G20210A mutations, and MTHFR C677T and PAI-1 polymorphisms were significant.

The risk of venous thrombosis is calculated as follows:

The risk of venous thrombosis = -2,4813 + 0,1105 × (HF according to NYHA classification) + 0,0031 × (weight) + 0,0124 × (age) — 0,2923 × (COPD) — 0,1344 × (early deaths in the family history) + 0,1960 × (factor V Leiden mutation) + 0,0042 × (asthma duration) + 0,2550 × (trauma) + 0,0126 × (height) + 0,3303 × (surgery) + 0,2300 × (combination of mutations) — 0,0041 × (AF duration) — 0,0915 × (CAD) + 0,2932 × (exacerbation of inflammatory bowel disease) — 0,1853 × (MTHFR C677T polymorphism) + 0,0018 × (diabetes duration) + 0,1000 × (prothrombin G20210A mutation) — 0,0101 × (polymorphism PAI-1), where:

— HF according to NYHA classification (0 — no HF, 1 — class I, 2 — class II, 3 — class III, 4 — class IV);

— weight, kg;

— age, years;

**Table 1**

**Regression coefficients for predicting the venous thrombosis**

| Factor | B | β |
|---|---|---|
| Constant | -2,481 | – |
| HF according to NYHA classification | 0,111 | 0,245 |
| Weight (kg) | 0,003 | 0,140 |
| Age, years | 0,012 | 0,441 |
| COPD | -0,292 | -0,458 |
| Early deaths in the family history | -0,134 | -0,095 |
| Factor V Leiden Mutation | 0,196 | 0,062 |
| Asthma duration | 0,004 | 0,114 |
| Trauma | 0,255 | 0,098 |
| Height (cm) | 0,013 | 0,220 |
| Surgery | 0,330 | 0,074 |
| Combination of mutations | 0,230 | 0,230 |
| Duration of atrial fibrillation | -0,004 | -0,113 |
| Coronary artery disease | -0,092 | -0,177 |
| Inflammatory bowel disease | 0,293 | 0,103 |
| MTHFR C677T polymorphism | -0,185 | -0,185 |
| Diabetes duration | 0,002 | 0,070 |
| Prothrombin G20210A mutation | 0,100 | 0,035 |
| PAI-1polymorphism | -0,010 | -0,008 |

**Note:** B — non-standardized coefficients, β — standardized coefficients.

— COPD (0 — No COPD, 1 — Stage I: mild COPD, 2 — Stage II: moderate COPD, 3 — Stage III: severe COPD, 4 — Stage IV: very severe COPD);

— early deaths in the family history (0 — no, 1 — yes);

— factor V Leiden mutation (0 — no, 1 — yes);

— asthma duration, years;

— traumas in history (0 — no, 1 — yes);

— height, cm;

— surgeries in history (0 — no, 1 — yes);

— combination of mutations (0 — no, 1 — yes);

— AF duration, years;

— CAD (0 — No CAD, 1 — atherosclerotic cardiosclerosis, 2 — old myocardial infarction, 3 — stable angina, 4 — vasospastic angina);

— exacerbation of inflammatory bowel disease (0 — no, 1 — yes);

— MTHFR C677T polymorphism (0 — no, 1 — yes);

— diabetes duration, years;

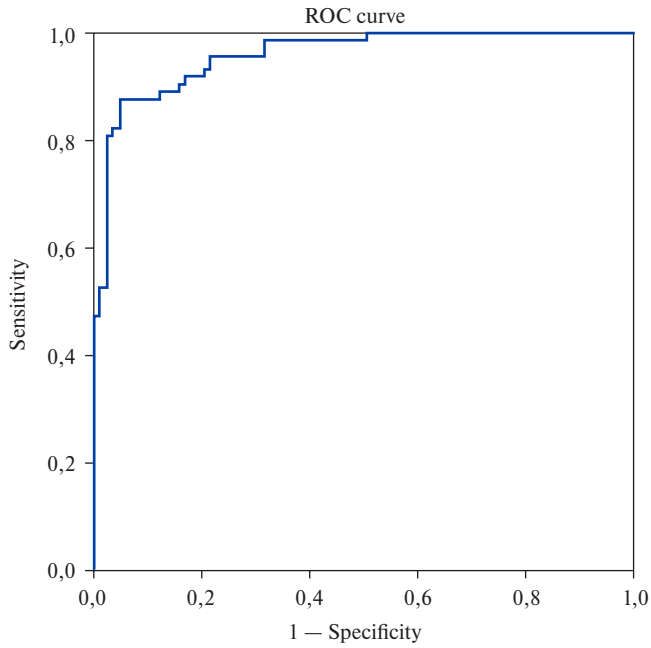


**Fig. 1.** ROC curve for predicting the venous thrombosis, taking into account congenital thrombophilia.
**Note:** area under the ROC curve — 95,9%

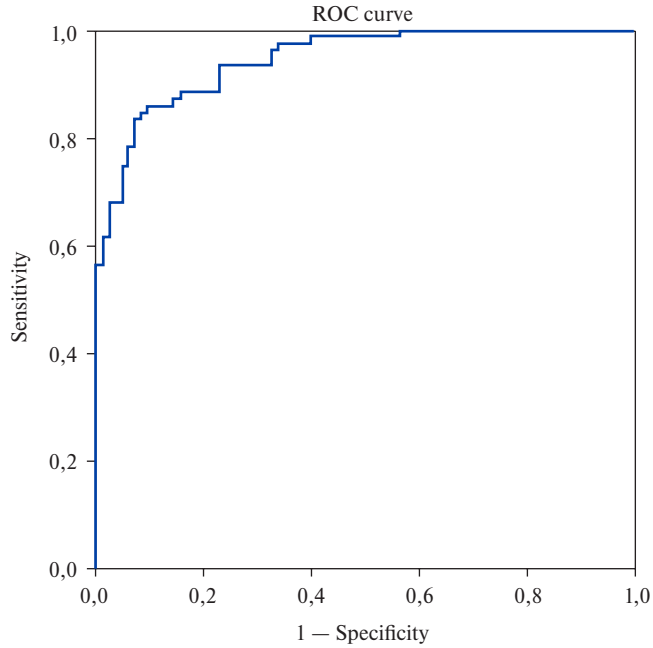


**Fig. 2.** ROC-curve for predicting the venous thrombosis without data on congenital thrombophilia.
**Note:** area under the ROC curve — 94,6%.

— prothrombin G20210A mutation (0 — no, 1 — heterozygous carriage, 2 — homozygous carriage);

— PAI-1 polymorphism (0 — no, 1 — yes).

This formula showed a sufficiently high forecast accuracy and clinical significance. To analyze the accuracy, the ROC curve was calculated (Fig. 1).

**Table 2**

**Distribution of patients with venous thrombosis by risk groups**

| Risk groups for venous thrombosis | | Thrombosis | | | |
|---|---|---|---|---|---|
| | | No | Yes | Overall | Proportion, % |
| Low | up to 0,2615 | 50 | 1 | 51 | 2,0 |
| Moderate | from 0,2615 to 0,45 | 24 | 7 | 31 | 22,6 |
| High | from 0,45 to 0,627 | 7 | 12 | 19 | 63,2 |
| Veri high | from 0,627 | 2 | 54 | 56 | 96,4 |

Low risk  Moderate risk  High risk  High risk

**Table 3**

**Risk levels of venous thrombosis in a virtual patient depending on the presence of mutations and increased BMI**

| Weight | BMI | No mutations | PAI-1 | MTHFR + PAI-1 | F2 G/A | F2 G/A + MTHFR | F2 A/A | F5 Leiden | F5 Leiden + MTHFR | F2 A/A + MTHFR | F2 G/A + PAI-1 | F2 A/A + PAI-1 | F5 Leiden + PAI-1 | F5 Leiden + F2 G/A |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Normal | 23,44 | 0,14 | 0,13 | 0,18 | 0,24 | 0,29 | 0,34 | 0,34 | 0,38 | 0,39 | 0,46 | 0,56 | 0,56 | 0,67 |
| Overweight | 26,56 | 0,17 | 0,16 | 0,21 | 0,27 | 0,32 | 0,37 | 0,37 | 0,42 | 0,42 | 0,49 | 0,59 | 0,59 | 0,70 |
| Class I obesity | 30,86 | 0,21 | 0,20 | 0,24 | 0,31 | 0,35 | 0,41 | 0,41 | 0,45 | 0,45 | 0,53 | 0,63 | 0,63 | 0,74 |
| Class II obesity | 35,16 | 0,24 | 0,23 | 0,28 | 0,34 | 0,39 | 0,44 | 0,44 | 0,48 | 0,49 | 0,56 | 0,66 | 0,66 | 0,77 |
| Class III obesity | 41,02 | 0,29 | 0,28 | 0,33 | 0,39 | 0,44 | 0,49 | 0,49 | 0,53 | 0,54 | 0,61 | 0,71 | 0,71 | 0,82 |

**Abbreviations**: F2 A/A — homozygous mutation in the prothrombin gene, F2 G/A — heterozygous mutation in the prothrombin gene, F5 Leiden — factor V gene mutation, MTHFR — methylene tetrahydrofolate reductase gene, PAI-1 — mutation in the plasminogen activator inhibitor-1gene.

Low risk  Moderate risk  High risk  High risk

Further, to modify the risk into the probability of thrombosis, we formed 4 risk groups to calculate the joint distribution of risk and presence of thrombosis (Table 2). In our study, 2% of patients with thrombosis were in the low-risk venous thrombosis group, 22,6% in the moderate-risk group, 63,2% in the high-risk group, and 96,4% in the very high-risk group.

Here are a few examples to demonstrate how the calculator works. Let us suppose that a 35-year-old patient (height — 160 cm, weight — 58 kg, body mass index (BMI) — 22,66 kg/m$^2$) has no congenital thrombophilia and concomitant pathology. In this case, RAM consider that the risk is 0,14. So, a patient has the low risk of venous thrombosis.

If a patient has excess body weight (height — 160 cm, weight — 68 kg, BMI — 26,56 kg/m$^2$), the risk of venous thrombosis will be 0,17 (low risk); in case of class I obesity (height — 160 cm, weight — 79 kg, BMI — 30,86 kg/m$^2$) — 0,21 (low risk); ); in case of class II obesity (height — 160 cm, weight — 90 kg, BMI — 35,16 kg/m$^2$) — 0,24 (low risk). Only class III obesity will lead to moderate-risk of venous thrombosis — 0,29 (height — 160 cm, weight — 105 kg, BMI — 41,02 kg/m$^2$). Consequently, in the absence of mutations, a patient is in the moderate-risk group of venous thrombosis only in class III obesity (Table 3).

If a patient is carrier of one mild mutation (for example, PAI-1 polymorphism), then the thrombosis risk depending on BMI will be about the same. In case of combination of two mild mutations (MTHFR C677T and PAI-1 polymorphisms) and class II obesity, a patient will go up to the medium-risk group.

Homozygous carriage of prothrombin G20210A and presence of factor V Leiden mutation will lead to a high risk of thrombosis in patients with class III obesity. Patients with combination of prothrombin G20210A or factor V Leiden mutations with MTHFR C677T polymorphism and normal weight or overweight will have the moderate risk of thrombosis, and in case of obesity, the risk will be high. In combination with PAI-1 polymorphism, the risk will be high in patients with normal weight and overweight, and in case of obesity, the risk will be very high. Patients with both prothrombin G20210A and factor V Leiden mutations will have very high risk for any body weight.

In addition to mutations and increased BMI, the thrombosis risk will be affected by age, the presence of CAD, HF, COPD, early deaths in family history, recent traumas and surgeries, inflammatory bowel disease, as well as the duration of asthma, AF and diabetes. So, if a patient with BMI=22,66 with a factor V Leiden mutation and PAI-1 polymorphism has type 2 diabetes for 3 years and asthma for 8 years, then the risk of venous thrombosis will be very high (0,63) even with overweight.

If a patient does not know about presence of the listed mutations, then it is possible to use a truncated RAM version (Table 4). The algorithm for calculating the risk of venous thrombosis is similar.

Using the current RAM, it is possible to calculate the individual risk of venous thrombosis (Table 5) and justify the need for thrombophilia screening to clarify the risk. For example, according to the truncated RAM version, a patient with class II obesity (height — 160 cm, weight — 90 kg, BMI — 35,16 kg/m$^2$) will have moderate risk of thrombosis (0,32). In this case, screening for thrombophilia is required to clarify the risk of venous thrombosis.

However, the full version of the calculator has a higher forecast accuracy (the area under the ROC curve — 95,9) compared to the truncated version (the area under the ROC curve — 94,6) (Fig. 2).

Both online RAM versions will be available at http://1mgmu.com.

## Discussion

VTE is a serious medical problem worldwide [1]. The risk of thrombosis in a patient depends on individual factors. An accurate assessment of the thrombosis risk is sometimes difficult for practitioners. In order to determine the need for prevention, there are

**Table 4**

**Regression coefficients for predicting the venous thrombosis by RAM version without thrombophilia**

| Factor | B | β |
|---|---|---|
| Constant | -2,488 | 0,224 |
| HF according to NYHA classification | 0,101 | 0,142 |
| Weight (kg) | 0,003 | 0,453 |
| Age, years | 0,013 | -0,482 |
| COPD | -0,312 | -0,104 |
| Early deaths in the family history | -0,148 | 0,103 |
| Asthma duration | 0,004 | 0,127 |
| Trauma | 0,334 | 0,22 |
| Height (cm) | 0,013 | 0,224 |
| Surgery | 0,332 | 0,074 |
| Duration of atrial fibrillation | -0,005 | -0,149 |
| Coronary artery disease | -0,089 | -0,174 |
| Inflammatory bowel disease | 0,345 | 0,131 |
| Diabetes duration | 0,009 | 0,074 |

**Note:** B — non-standardized coefficients, β — standardized coefficients.

**Table 5**

**Risk groups for venous thrombosis by RAM version without thrombophilia**

| Risk groups for venous thrombosis | | Thrombosis | | | |
|---|---|---|---|---|---|
| | | No | Yes | Overall | Proportion, % |
| Low | up to 0,32 | 55 | 2 | 57 | 3,5% |
| Moderate | from 0,32 to 0,49 | 20 | 9 | 29 | 31,0% |
| High | from 0,49 to 0,66 | 6 | 14 | 20 | 70,0% |
| Veri high | from 0,66 | 2 | 53 | 55 | 96,4% |

Low risk Moderate risk High risk High risk

many scores, calculators and RAM for venous thrombosis. The most famous RAMs are: 4-Element RAM, Caprini RAM, the full logistic model, Geneva RISK Score, IMPROVE-RAM, Kucher Model, Multivariable Model, Padua Prediction Score, QThrombosis Risk Calculator. Ideal RAM should be tested by external studies to identify patients with high VTE risk, improve thromboprophylaxis and outcomes, and be cost-effective [10]. It should not contain too many criteria and should be easily applicable in clinical practice [11]. None of the current RAMs meets these criteria [10]. Potential limitations of most RAMs include the lack of prospective validation, applicability only to high-risk subgroups, and high complexity of use [12].

Almost all RAMs included factors such as a history of VTE, prolonged immobilization, central venous catheter, cancer, old age, trauma, surgery, hormone replacement therapy or oral contraceptives. Arterial thrombosis as risk factor is taken into account in the Caprini RAM, Geneva Risk Score and Padua Prediction Score. Concomitant pathologies such as HF, COPD, and inflammatory diseases of the joints and intestine were taken into account in the Caprini RAM, Geneva Risk Score, Padua Prediction Score, and Multivariable Model. Obesity (BMI >30) considered as a risk factor in each RAM, except for IMPROVE-RAM and 4-Element RAM. The Caprini RAM assessed the presence of thrombophilia, such as factor V Leiden and prothrombin G20210A mutations, high homocysteine level, and lupus anticoagulant [10]. Padua Prediction Score took into account deficiency of antithrombin, proteins C or S, as well as factor V Leiden and prothrombin G20210A mutations [13]; IMPROVE-MPP — deficiency of antithrombin, proteins C or S, factor V Leiden and prothrombin G20210A mutations, and antiphospholipid syndrome [14]. The presence of thrombophilia was also assessed in the Geneva Risk Score and Multivariable Model [10].

External testing was carried out by Padua Prediction Score, Geneva Risk Score, Kucher Model, where thromboprophylaxis appointment improvement was shown [15]. In prospective studies, only Geneva Risk Score, Padua Prediction Score, and IMPROVE-RAM were assessed.

We developed a calculator taking into account both known risk factors, and congenital thrombophilia and concomitant pathology. The thromboprophylaxis should be considered at high individual risk (>0,45) of venous thrombosis. According to our truncated RAM version, patients without diagnosed thrombophilia and with moderate venous thrombosis risk needs thrombophilia screening to clarify the risk

## Conclusion

The advantages of our RAM are a small number of factors necessary for assessing the risk, considering of four thrombophilias and online access. Unfortunately, our RAM has some limitations. Our monocentric study included a small number of patients. Despite this, the obtained formula showed a high forecast accuracy and clinical value. However, to verify the effectiveness of our RAM, an external prospective study is necessary. We believe that this RAM will help practitioners solve problems with thromboprophylaxis and minimize errors.

**Conflicts of Interest:** nothing to declare.

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# Role of cognitive impairments and decreased muscle strength in cardiovascular mortality of 55 years and older population

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**Aim.** To assess possible associations of impaired cognitive function (CF) with muscle strength, determined using handgrip test, as well as their role in cardiovascular mortality (CVM) in a population of 55 years and older.

**Material and methods.** This work was carried out in the framework of the prospective cohort study "Stress, aging and health". During the study 1876 men and women aged 55 and older were examined. CF was estimated on the Mini-Mental State Examination (MMSE) scale, the decrease of CF was recorded with scores of less than 24 points (overall 30 points). Muscle strength was estimated according to handgrip test. To assess the role of muscle strength in CVM, handgrip test values, corresponding to the first quintile, were used — less than 19 kg for women, and less than 32 kg for men. Mortality was estimated on the basis of death register using standard methods. During the observation, 247 deaths from cardiovascular diseases were recorded.

**Results.** The study included 1876 participants aged 55 years and older (48% of men and 52% of women). CF parameters according to the MMSE questionnaire were within the normal range of more than 80% of those examined. According to the results of the regression analysis, only low values of handgrip test (at the level of 1 quintile) were reliably associated with cognitive impairments ($p<0,05$). These associations were more pronounced in women (odds ratio (OR): 3,17; 95% CI 1,31- 7,69), compared with men (OR: 2,41; 95% CI 1,05-5,54). In 55 years and older men, cognitive impairments were significantly associated with CVM (OR: 1,97; 95% CI 1,40-2,78) and reduced muscle strength (OR: 1,63; 95% CI 1,18-2,25). Among women, only reduced muscle strength significantly increased the risk of CVM (OR: 1,77; 95% CI 1,19-2,61). The simultaneous presence of these pathologies was reliably associated with CVM.

**Conclusion.** The presented study revealed significant associations of cognitive impairments with reduced muscle strength. The presence of both pathological disorders is prognostically unfavorable for cardiovascular death in a population of 55 years and older (both among men and women). Thus, it is recommended to consider the possibility of including of muscle strength and cognitive functioning assessment in prognostic scales.

**Key words:** cognitive function, muscular strength, mortality, cardiovascular diseases, population 55 years and older.

**Conflicts of Interest:** nothing to declare.

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It is known that the prevalence of decreased cognitive function (CF) increases with age [1]. At the same time, every tenth one suffering from cognitive impairment has dementia in old age [2, 3]. In itself, cognitive pathology leads to functional disorders, quality of life decrements, and is also associated with premature mortality [4, 5].

According to studies conducted in different years, several risk factors of cognitive impairment were identified, such as old and senile age, lack of family, hypertension, diabetes and a low level of education [6]. Later, regarding to some of above-mentioned factors, contradictory and even paradoxical effects were presented. In particular, this concerned hypertension and high blood pressure (BP) [7, 8]. Conversely, factors that can prevent cognitive impairment in the elderly were also identified (for example, high physical activity) [9, 10].

Regular physical activity helps maintain normal body weight, muscle function, and reduces the risk of falls and fractures in the elderly. On the contrary, insufficient physical activity along with age is one of the main determinants of a muscle strength decrease [11]. One of the safest and easily reproducible methods for assessing muscle strength in the elderly is handgrip test [12]. At the same time, low values of muscle strength, measured by handgrip test, according to some reports, increase the risk of cardiovascular diseases (CVD), as well as all-cause and cardiovascular (CV) mortality [13-15].

However, there are only a few Russian studies that assessed the associations of cognitive functioning and handgrip strength test with CV mortality in middle-aged and older people. The aim of this study was to assess the contribution of cognitive impairment and decreased muscle strength, measured by handgrip test, to CV mortality in Muscovites of 55 years and older.

## Material and methods

This research was conducted in the framework of the prospective cohort study "Stress, Aging and Health in Russia" (SAHR), carried out at National Medical Research Center for Preventive Medicine (Moscow, Russia), with the direct involvement of the Max Institute for Demographic Research Planck (Rostock, Germany) and Duke University (Durham, USA). This study was approved by the Independent Ethics Committee of the National Medical Research Center for Preventive Medicine and the Expert Council of Duke University. In the period from 2007 to 2009, all participants were examined at the National Medical Research Center for Preventive Medicine. The assessment included questionnaire survey developed by the epidemiology department of the National Medical Research Center for Preventive Medicine with the participation of international experts [16]. The analysis included such socio-demographic parameters as gender, age, education (below secondary, secondary and above secondary) and marital status (never married, married, divorced (or separated) and widower/widow). CF was assessed using the Mini-Mental State Examination (MMSE), a decrease in which was recorded with scores less than 24/30. Blood pressure was measured on the right hand twice in a sitting position using an Omron HEM-712 electronic automatic tonometer. Hypertension (HTN) was established in systolic blood pressure ⩾140 mm Hg or diastolic blood pressure ⩾90 mm Hg, or in the case of taking antihypertensives. The diagnosis of stroke and diabetes was established by the questionnaire. Alcohol intake status was determined depending on the consumption of alcoholic beverages during the last year. Muscle strength was evaluated according to handgrip test. This test was performed

**Table 1**

**Gender characteristics of study participants**

| Parameter | Men (n=898) | Women (n=978) |
|---|---|---|
| Age (years) | 69,4 (±8,14) | 67,7 (±7,26) |
| Education (%) | | |
| primary | 13,9 | 8,1 |
| secondary | 37,2 | 39,1 |
| higher | 48,9 | 52,9 |
| Marital status (%) | | |
| never married | 1,5 | 7,1 |
| married | 79,7 | 42,2 |
| divorced | 7,2 | 15,8 |
| widower/widow | 11,7 | 35 |
| Alcohol consumption (%) | 71,6 | 34 |
| Hypertension (%) | 75,0 | 72,3 |
| History of stroke (%) | 10,3 | 5,9 |
| History of diabetes (%) | 10,3 | 12,2 |
| Reduced EF (%) | | |
| 55-64 years old | 8,2 | 6,2 |
| 65-74 years old | 11,82 | 9,1 |
| 75-84 years old | 29,6 | 29,5 |
| 85 years and older | 50,0 | 41,7 |
| Muscle strength measured by handgrip test (kg) | | |
| 55-64 years old | 43,0 | 24,6 |
| 65-74 years old | 38,1 | 22,2 |
| 75-84 years old | 32,5 | 18,4 |
| 85 years and older | 27,3 | 16,2 |

**Table 2**

**Associations between reduced EF and muscle strength measured by handgrip test* among men and women**

| Quintiles of muscle strength (M/W) | OR | 95% CI | p | OR | 95% CI | p |
|---|---|---|---|---|---|---|
| | Men (n=898) | | | Women (n=974) | | |
| Q1 (<32 kg/<19 kg) | 2,41 | 1,05-5,54 | 0,03 | 3,17 | 1,31-7,69 | 0,01 |
| Q2 (32-36 kg/19-21 kg) | 1,46 | 0,64-3,32 | 0,36 | 2,51 | 0,99-6,36 | 0,05 |
| Q3 (37-40 kg/22-24 kg) | 1,50 | 0,65-3,45 | 0,35 | 2,09 | 0,82-5,32 | 0,12 |
| Q4 (41-45 kg/25-27 kg) | 0,89 | 0,36-2,22 | 0,80 | 1,56 | 0,57-4,25 | 0,39 |
| Q5 (>45 kg/>27 kg) | 1 (reference range) | | | 1 (reference range) | | |

**Note:** * Q1-Q5 — quintiles of muscle strength; data are given after adjusting for age, education, marital status, alcohol use, hypertension presence, stroke and diabetes.
**Abbreviations:** OR — odds ratio, CI — confidence interval.

three times with each hand in a standing position. The final analysis used the maximum values obtained during the survey. Mortality was estimated on the basis of a mortality register using standard methods. During the observation, 411 deaths were recorded, including 247 as a result of CVD. To assess the contribution of muscle strength to CVD mortality, values of handgrip test corresponding to the first quintile were used — less than 19 kg for women and less than 32 kg for men.

Statistical analysis of the results was performed using the STATA® Software. Methods of standard descriptive statistics, such as calculating of average values, standard deviations and standard errors, and rank statistics were used. Associations were evaluated using logistic regression; mortality was studied using the Cox proportional hazards.

## Results

The study included 1876 participants aged 55 years and older, including 898 (48%) men. Table 1 presents the socio-demographic characteristics, as well as the prevalence of risk factors for the study population included in the analysis. The average age of the subjects was 68,4 (±7,6) years. More than half of the participants had higher education (51%) and at the time of assessing were married (60%). Gender differences in marital status are noteworthy: men are less likely to be single, they are much more likely to be married than women, less divorced and almost three times less likely to remain widowers. HTN was diagnosed in 70% of participants, while about 8% had a history of stroke.

According to the MMSE questionnaire, CF parameters were within normal limits for more than 80% of subjects. As expected, the prevalence of cognitive impairment increased with age. So, if in the group of 55-60 years old people every tenth one suffered from cognitive impairment, then in the group of ⩾85 years already half of the participants had this pathology. Along with a CF decrease, muscle strength measured by handgrip test decreased with age.

The results of a regression analysis of associations between cognitive impairment and muscle strength measured by handgrip test, after adjusting for age, education, marital status, alcohol intake, HTN, stroke and diabetes are presented in Table 2. It was revealed that only low values of handgrip test (at quintile level 1) were significantly associated with cognitive impairment (p<0,05). These associations were more pronounced in women (odds ratio (OR): 3,17; 95% confidence interval (CI) 1,31-7,69) compared with men (OR: 2,41; 95% CI 1,05-5,54).

According to the proportional risk analysis (Table 3), after adjusting for age, socio-demographic indicators and risk factors, it turned out that in a population of men ⩾55 years, cognitive impairment was significantly associated with CV mortality (risk ratio (RR): 1,97; 95% CI 1,40-2,78) and decreased muscle strength (RR: 1,63; 95% CI 1,18-2,25). In a female cohort of the same age, only decreased muscle strength significantly increases the risk of CV mortality (RR: 1,77; 95% CI 1,19-2,61). Regardless of gender, after adjusting for age and other risk factors, the combination of cognitive impairment and decreased muscle strength was significantly and independently associated with CV mortality (p=0,01).

## Discussion

The etiology of age-related dementia is not fully understood, but there is no doubt that it is multifactorial disease. The difficulty lies in the fact that some parameters, in addition to being risk factors, may be the results of dementia. For example, meta-analysis

**Table 3**

**Contribution of cognitive impairment and decreased muscle strength to cardiovascular mortality**

| Parameter | Model 1[a] | Model 2[b] | Model 3[a] | Model 4[b] |
|---|---|---|---|---|
| | Men | | Women | |
| | HR (95% ДИ) | HR (95% ДИ) | HR (95% ДИ) | HR (95% ДИ) |
| Reduced CF | 2,01 (1,43-2,81)* | 1,97 (1,40-2,78)* | 1,61 (1,01-2,56)* | 1,40 (0,87-2,27) |
| Reduced MS | 1,80 (1,32-2,45)* | 1,63 (1,18-2,25)* | 1,93 (1,31-2,86)* | 1,77 (1,19-2,61)* |
| Reduced CF+MS | 2,03 (1,48-2,79)* | 1,91 (1,38-2,64)* | 1,90 (1,27-2,85)* | 1,66 (1,10-2,51)* |

**Note:** [a] — after adjusting for age and education, [b] — after adjusting for age, education, marital status, alcohol use, hypertension presence, stroke, diabetes, risk factors, * — p<0,05.

**Abbreviations:** MS — muscle strength, CF — cognitive function.

by Rockwood K. and Middleton L. (2007) showed that low physical activity, being a risk factor for obesity, diabetes and HTN, together with these diseases leads to cognitive impairment [17]. On the other hand, some authors believe that cognitive impairment itself can lead to decreased physical function and muscle strength. For example, according to Rosso AL, et al., decreased motion in some older people may be associated with cognitive impairment [18]. According to other authors, reduced muscle strength is not a risk factor, but an early marker of CF reduction [19]. However, all authors agree that CF decrease is associated with low physical activity and low muscle strength.

The results of this study are consistent with data obtained previously by foreign researchers. So, in a recent study by Vancampfort D, et al. it was shown that in the middle-aged and older population, low muscle strength measured by handgrip test is significantly associated with cognitive impairment, regardless of gender, age and other risk factors [20]. In conclusion, the authors write that further studies are likely to provide evidence that low muscle strength is a clinically reliable marker for CF disorders, and the development and implementation of exercise programs will allow modifying cognitive health along with physical. Although we share this view, the results of our study do not allow us to determine whether muscle strength measured by handgrip test is a risk factor for cognitive impairment or a result of this pathology. That is because the study of the associations between cognitive impairment and low muscle strength was carried out on the data of one-time survey. Further prospective studies are required to clarify the nature of the interaction of cognitive function and muscle strength.

At the same time, we obtained significant associations between decreased muscle strength and CV mortality among men and women, while the contribution of reduced CF to CV mortality in a multivariate model was significant only in the male cohort.

In recent decades, a number of studies devoted to the effect of cognitive impairment on CV mortality were conducted. However, the results of these studies regarding the elderly population are often controversial. So, in a study by Ji An, et al. significant associations between cognitive impairment and all-cause and CV mortality have been shown [21]. However, Kerola T, et al. found that the contribution of reduced CF to CV mortality remained significant only after adjusting for gender and age, while in the multivariate model this parameter became insignificant [22]. As for the associations of decreased muscle strength and mortality, the results of studies in this field indicate the significant prognostic value of this risk factor. Moreover, some authors propose using this parameter as an indicator of the elders' health in clinical practice [23].

Thus, the results of our analysis showed that with a decrease in muscle strength in people ⩾55 years of age, we can expect a decrease in CF three times more often in women and 2 times more often in men compared to those with high values of handgrip strength test (Q5).

Low muscle strength along with both pathological disorders, is the most unfavorable prognostic factor for CV mortality in the male and female population of the studied age. An isolated CF decrease increases the risk of death only in men. Given the results obtained, inclusion an assessment of muscle strength and CF as independent risk factors in the practical prognostic scales should be considered.

**Conflicts of Interest:** nothing to declare.

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# Hypertension specific patient-reported outcome measure. Part II: validation survey and item selection process

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**Aim.** Improvement of the health-related quality of life (HRQoL) is one of the basic principles of value-based medicine. HRQoL could be assessed by the patient reported outcome measures (PROMs) also in case of arterial hypertension (HTN). However for HTN patients only generic PROMs are still used. Previously the group of experts had created the primary version of HTN-specific PROM. The purpose of the second part was to conduct a validation survey and to select the items in a statistically-based manner.

**Material and methods.** Validation survey was conducted in a large multidisciplinary center among patients with HTN stages 1-3 and healthy volunteers. Inclusion criteria were age >18 years old, ability to understand or complete the scale themselves, absence of significant illness requiring hospitalization. The items were selected according to the principles of classical test theory (CTT) and item response theory (IRT). The criteria for CTT were sensitivity (standard deviation and coefficient of variation with corresponding confidence intervals), representativeness (item-total Pearson's correlation coefficient), internal consistency (Cronbach's $\alpha$ coefficient). In IRT analysis two methods were adopted — value of four degrees of difficulty and the discrimination estimate. Each question was evaluated according to 8 criteria. An item was considered for selection when it was retained by $\geqslant$4 criteria. The expert panel considered practical significance of each item.

**Results.** A total of 430 questionnaires were distributed and 407 (94,7%) of them were returned completed (from 359 hypertensive patients, mean age 62,3±11,7 y.o.; 48 healthy volunteers, mean age 38,8±10,5 y.o.). The average time for PROM filling was 24±4,2 minutes. Of 163 questions, 27 met all 8 criteria and 3 questions did not match any of the 36 HTN-specific questions, 11 matched $\geqslant$5 criteria and in the generic part there were 87 questions (33 in the PHY domain, 35 for PSY, 8 for SOC, 11 for THER). The symmetric distribution of criteria was seen in 25 questions, of which 11 were evaluated by experts and then retained. For 40 questions, <4 eligibility criteria were recorded, of which 9 were retained after expert review. The PROM draft contained 80 questions (19 questions in the physiology domain, 22 in psychology, 6 in social, 13 in therapy, 20 items are HTNspecific).

**Conclusion.** The methods of CTT and IRT allowed to reduce the PROM volume without losing the semantic richness and the need to reorganize the conceptual structure. The next step is the validation of the scale.

**Key words:** arterial hypertension, patient-reported outcome measures, health related quality of life, questionnaire, classical test theory, item response theory.

**Conflicts of interest:** nothing to declare.

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Hypertension (HTN) as the leading cause of premature mortality and disability [1], is predicted to maintain a leading position until 2040 [2]. Undoubtedly, the main aim of health care is to save and prolong life. However, improving of life quality (reduce the severity of symptoms, lighten the psychological and social burden of diseases) is equally important. Like most chronic pathologies, HTN affects the quality of life (QOL) associated with health in the range from insignificant to quite significant [3]. This fact is of particular interest since there are more than a billion HTN patients around the world, the effectiveness of treatment in most of which is insufficient [4].

Recent scientific evidence detects a decrease in QOL of patients with uncontrolled HTN; however, even with undoubted effectiveness of some antihypertensive drugs and rational treatment regimens, it can also negatively affect QOL [5]. To "measure" the symptoms and influence of the disease on the psychological, social fields of the patient's life is possible due to patient-reported outcome measures (PROMs) — a highly effective tool for translating subjective perception into an objective assessment.

Since the use of PROMs in routine clinical practice allows you to change the paradigm of decision taking, making it more personalized, it is expected that medical care can be better also at population level. Thus, international and Russian guidelines for the management of HTN patients are general in nature and are based on the "crude" stratification of patients according to the main objective parameters [6]. In turn, PROMs is a more holistic and comprehensive assessment of QOL and the treatment effect from the patient's point of view. PROMs analysis can provide the doctor with valuable information for implementing the precision medicine. It is also worth noting that sometimes the results of PROMs analysis are the primary endpoints of clinical trials, replacing or complementing the "conventional" objective and laboratory goals.

Detailed algorithms for developing tools of QOL assessing are given in the international guidelines. However, many researchers have noted the difficulties in choosing a suitable PROM, since it often depends on a specific pathology, clinical trial and goals of the authors/experts. As with many chronic pathologies, patients with HTN are in a certain conditions' continuum, determined by the degree of severity (which can be significantly alleviated in a short time) and stage (almost unmanageable). Therefore, it is important to have reliable and concise questionnaires for patients with a certain pathology. In addition, using adequate data obtained with the help of disease-specific PROMs, it becomes possible to carry out cost-utility analysis [7]. It is one of the most complex and sophisticated methods of economic analysis, which is most important in the value-based healthcare (clinical, economic and patient-oriented benefits).

At first stage, the process of creating a multidimensional and multivariate disease-specific PROM for HTN patients was described [8]. As the first part of study, Interviewing and pilot questioning of patients were carried out, followed by assessment of the questionnaire structure, which greatly reduced it. The current stage is aimed at use of special statistical methods for the analysis of psychological tests, which complement the qualitative examination.

## Material and methods

The study was conducted in accordance with the Good Clinical Practice standards and Declaration of Helsinki principles. The study protocol was approved by the local Ethics Committee. Prior to inclusion in the study, all participants gave written informed consent. The guidelines and documents of Food and Drug Administration (FDA) [9], the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [10], and the International Society for Quality of Life Research (ISOQOL) were used for PROM creation and validation [11]. The study was supported by a grant from the Russian Science Foundation (project № 17-15-01177).

**Validation study.** The survey with the primary PROM version [8] was conducted in an outpatient department of a large multidisciplinary medical center.

The main group consisted of patients with stage 1-3 HTN who were first seen by a hypertensiologist (one of the authors), while the antihypertensives' status was not taken into account. The second group of participants was conditionally healthy volunteers.

The general inclusion criteria were at least 18 years of age, the ability to understand the purpose and instructions for filling out, independently read and answer the questions in the print PROM form.

The main exclusion criteria were a cognitive deficit assessed by a physician subjectively or a diagnosis of grade 2 or higher encephalopathy, a serious somatic pathology (cardiovascular or non-

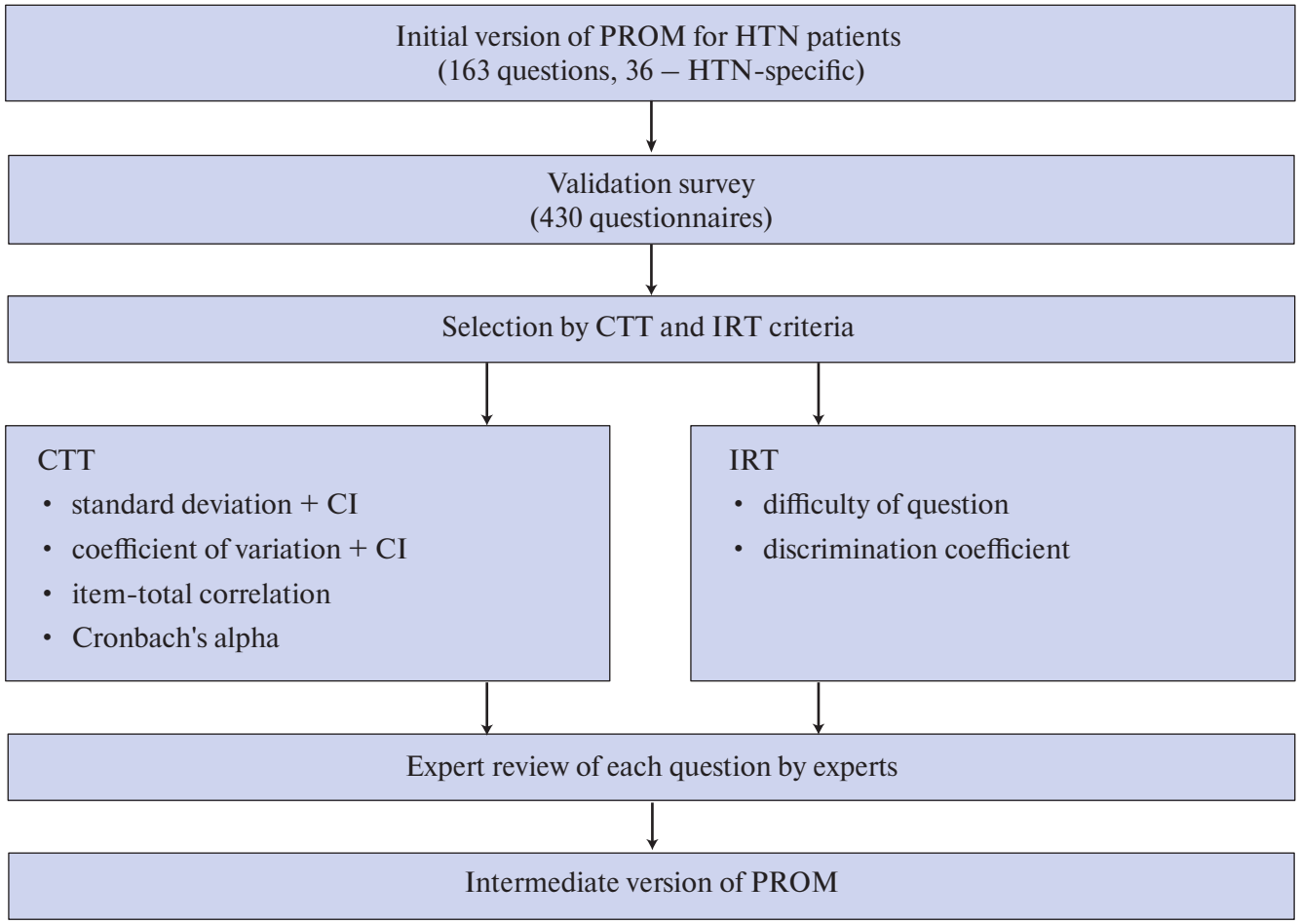


**Fig. 1.** The design of the second stage of the PROM development for HTN patients.
**Abbreviations:** PROM — patient-reported outcome measure, HTN — hypertension, CTT — classical test theory, IRT — item response theory, CI — confidence interval.

cardiac), which required hospital (including surgical) treatment in the near future. All participants were asked to fill out a questionnaire after talking with a doctor and completing an informed consent form.

**Statistical analysis.** The selection of questions was based on the classical test theory (CTT) and item response theory (IRT).

When selecting questions by CTT, the following 6 criteria were used:

1. The sensitivity of the item was determined by standard deviation (SD). A question considered inappropriate if SD was <1,0.

1.1. Values of 95% confidence interval (CI) of SD >1,0 was the criterion of acceptability. Preferably, the lower confidence limit meets these requirements.

2. A question sensitivity was also evaluated using the coefficient of variation (CV) of responses; CV >20 units was required to remain question in the intermediate questionnaire version.

2.1. Similar to the CI for SD, the same requirements were used on the 95% CI for CV; the lower confidence limit was supposed to be >20 units.

3. Question representativeness was evaluated based on the item-total correlation. A question was considered appropriate if the Pearson's correlation coefficient between the mean value of the responses of a question and its area exceeded the CV=0,5.

4. Internal consistency was determined by Cronbach's alpha, which should have exceeded 0,5.

When selecting questions by IRT, 2 criteria were used, the values of which were estimated by maximum likelihood method:

1. Discrimination estimate (coefficient a). The key principle was as follows: the higher the coefficient a, the higher the item informative value. If

the coefficient value exceeded the a>0,5, then a question was remained in the questionnaire.

2. Value of difficulty degree, determined by four coefficients b1, b2, b3 and b4 and satisfying the inequality b1<b2<b3<b4. In this case, the values of b1 and b4 should have been in the range from -3 to +3. Questions where the values of these items fell outside this range, was removed from the questionnaire, since the distribution of answers to them would be shifted to one of the extremes (responses with points 1 or 5).

Each question was evaluated based on the eight criteria described above. If an item meets with four or more ones, then it could be maintain in the questionnaire. In addition, the significance and semantic richness of a question were reassessed by expert group. Thus, with the both use of statistical analysis and expert review, the logic and informative value of the second intermediate PROM version were formed (Fig. 1).

Statistical processing of the results was performed using the non-profit open source software package R Statistics (ver. 3.1.0, The R Foundation for Statistical Computing, Vienna, Austria) and the SPSS software package (ver. 23.0, IBM, Chicago, IL, USA). The level of statistical significance for differences was set as p<0,05. The following specialized programs were also used: IRTShiny Version 1.1 (http://kylehamilton.net/shiny/IRTShiny/); Classical Test Theory (Item Analysis) – http: //kylehamilton.net/shiny/CTTShiny. The jamovi software (https://www.jamovi.org/) was used for the reliability analysis.

## Results

The questionnaire survey involved 430 people. Overall 407 participants completed PROM forms: 359 — HTN patients: mean age — 62,3±11,7 years, 56,8% — women; stage 1 HTN — 139 patients, stage 2 HTN — 136 patients, stage 3 HTN — 84 patients; 48 — healthy volunteers (mean age — 38,8±10,5 years, 70,8% — women). The questionnaire completion rate was 94,7%, and the average completion time was 24±4,2 minutes (for HTN patients, since healthy volunteers did not answer questions regarding treatment). All respondents who completed the questionnaire and who were able to conduct a post-test interview (n=128), informed the clinical investigator that the questions and response options were correctly formulated and did not cause difficulties.

Analysis of the frequency distribution showed that there were 11,4% of unanswered questions. The missing data was analyzed by the Little's Test of Missing Completely at Random: $\chi^2$=347, p=0,39. Results showed that the distribution is consistent with normal, and omissions are random. Missing data was recovered by multiple imputation method.

The initial version of the questionnaire, formed by conceptual framework, consisted of a general ("non-specific") part, which included areas of "physiology" (PHY) with 43 questions (5 subareas: physical symptoms, general well-being and vitality, self-assessment, the limiting effect of physical health , dynamics of physical health), "psychology" (PSY) with 42 questions (5 subareas: emotional and behavioral symptoms, cognitive symptoms, psychological well-being, the limiting effect of mental health, dynamics of mental health). General part also included "social" area (SOC), which contained 15 questions (4 sub-area: social frustration, social resources, the effect of physical and mental health on social activity), and the "therapy" domain (THER) with 27 items (6 sub-areas: therapy satisfaction, therapy-related physical changes, therapy-related psychological changes, the effect of the treatment regimen on daily life, adherence to treatment). HTN-specific part included 13 questions in PHY and THER subdomains similar to the general part, 4 questions in PSY and 6 in SOC subdomains).

Thus, a total of 163 questions were assessed (36 questions regarded only HTN). For each question, the CTT and IRT criteria values are presented in Table 1. Twenty seven questions met all 8 criteria (2 questions of HTN-specific, 20 in the PHY area, 4 in the PSY area, 1 in the SOC area). Despite satisfactory values, questions PHY_4_3, PHY_4_5, and PHY_4_8 were removed due to low practical significance, questions PHY_4_10 and PHY_4_12 — due to duplication. PHY_4_14 and PHY_4_17 questions were not included in the intermediate version because similar questions were in the HTN-specific part (HTN_SOC_5, HTN_SOC_7, respectively). The following three questions did not meet any of the criteria: THER_6_7 "How often do you take medicine on friend recommendations or on your own without prescription?", THER_7_1 "How often do you miss scheduled appointments with a doctor?", HTN_THER_14 "How often do you eat fast food. These questions were excluded from the intermediate version of the questionnaire.

Eleven questions of the HTN-specific part met ⩾5 criteria; there were 87 such items in the gen-

eral part (33 were in the PHY domain, 35 — in the PSY area, 8 — in the SOC area, 11 — in the THER domain). After consistent expert review, 3 questions were removed from the HTN-specific part (HTN_SOC_4, HTN_THER_10, HTN_THER_11) due to low practical significance. In addition to the already mentioned items, 28 following ones were excluded from the general part: 7 PHY questions (practical insignificance, duplication of the HTN-specific part, discrepancy with the HTN concept), 15 PSY questions (low reliability, practical insignificance), 3 SOC questions (practical insignificance, duplication of the HTN-specific part); 3 THER questions (practical insignificance, duplication of the HTN-specific part).

Symmetric distribution of criteria was observed in 25 questions (9 — HTN-specific). These questions were reassessed by the authors, as a result of which 11 ones (HTN — 5, PSY — 1, THER — 5 questions) were remained in the intermediate version (due to the semantic richness and practical significance).

Forty questions did not meet at least 4 criteria (except for the three questions described above); 9 of them were remained after an expert review due to practical significance (7 — HTN-specific, questions PSY_5_5 and SOC_1_1 in the relevant areas).

Forty six questions (21 — HTN-specific) did not meet both basic statistical criteria of CTT and IRT (reliability and difficulty, respectively). Only 16 of them were remained in in the intermediate version of the questionnaire (11 — HTN-specific, 2 — PSY and THER, 1 — SOC) due to their practical significance and semantic richness.

Due to significant reduction of question pool and to facilitate the validation, HTN-specific questions were integrated into the relevant areas of the general part. Thus, the questions HTN_PHY_1-12 remained in the sub-area "physical symptoms"; items HTN_PSY_1-4 constituted an additional sub-area of "hypo- and hypernosognosia" in the PSY domain; HTN_SOC_3 were added to the sub-area "social resources in the HTN treatment", and questions HTN_SOC_5,7 — to the sub-area "the effect of physical health on social activity"; questions HTN_THER_1,2 were included in the subdomain "therapy satisfaction", HTN_THER_3-5 were included in the subdomain "adherence to treatment". The sub-areas "dynamics of physical health", "the effect of mental health on social activity" were removed from the intermediate version of PROM. As a result, the intermediate version included 80 questions (19 — PHY, 22 — PSY, 6 — SOC, 13 –THER, and 20 HTN-specific items) (Annex 1).

## Discussion

Expert selection, creating a conceptual framework and developing a questionnaire are some of the most important and difficult steps. However, when these steps are taken, it becomes necessary to select meaningful, practically significant, most reliable questions. An important step in the second part of the study was the need to obtain a sufficient amount of data for statistical analysis.

The most common method of social and psychological research is a mass survey. This is particularly important when developing new PROM or adapting well-known foreign-language ones, since the contribution of patients and the subsequent interviewing is one of the ways to confirm content validity [9]. Therefore, HTN patients, especially ambulatory ones, were broadly covered in the conditions close to the real clinical practice. Nevertheless, the mass survey inevitably leads to incomplete data, which is often associated with the unattainability, fatigue or inattention (when completing large questionnaires), cultural, ethnic and social characteristics of individuals [12]. The main reason for the loss of a tenth of the required data, according to the Little's MCAR test, was the fatigue or inattention of the respondents.

The resulting data pool of responses became the basis for evaluating each unit of the HTN-specific PROM according to both CTT and IRT.

CTT methods, also called true score theory, are clear and readily available for use. The main criteria of CTT in this work were considered SD and reliability. It should be noted that the authors did not evaluate the factor loading due to the large number of questions, areas and sub-areas. So, the probability of unreliable distribution by factors was rather high. For the Hyper-PRO questionnaire, an exploratory factor analysis was carried out within the initial selection of questions [13]. That was reasonable due to small initial pool.

It should be noted that despite the CTT recognition, it does not take into account latent traits and abilities of the respondents, and therefore the reliability assessment may be inadequate. In addition to CTT, an IRT method was used, based on item characteristics curves and difficulty of questions. CTT has three advantages over IRT: the

assessment of respondent's capacity does not depend on a specific question; the assessment does not depend on the study population; the accuracy of capacity assessment can also be determined. When using CTT, it is possible to determine the nonlinear relationship between the respondent's response and its potential quality, or to describe the relationship between the response and the factor underlying the question. However, CTT principles are rather difficult to understand and therefore the application is limited mainly by the teaching tests [14].

Reliability, size and content are important characteristics affecting the CTT application for PROM development. There is a growing understanding among specialists that combinations of quality questions can contribute to the development of the most valid and concise PROMs that would reduce the "respondent burden". Therefore, attempts are being made not to evaluate the PROM as a holistic concept, but to determine the reliability and importance of questions based on the characteristics of the patients' response. The active introduction of CTT and computer programs for adaptive testing made it possible to create a PROMIS system (Patient-Reported Outcomes Measurement Information System). From a large database of questions, a small number of the most informative items are selected based on the patient's characteristics. [15].

Most of the questions were removed on the basis of CTT and IRT combination. However, the items that were significant for the overall structure, despite that some of them did not meet the criteria, were remained based on the expert review. For example, most of the inappropriate questions of the HTN-specific part were remained, and the questions of the last THER subdomain (in the general and HTN-specific parts) were excluded; the sub-area "adherence to treatment" was significantly reduced. Items of this area were developed based on the clinical judgment of the authors and the theoretical problems of treating HTN patients. Probably, cultural, sociological and age-related characteristics, along with sample bias could be associated with the insufficient compliance with the selection criteria.

## Conclusion

The development of a disease-specific questionnaire based on the outcomes reported by HTN patients passed the second stage using the CTT and IRT methods and expert review. The results obtained led to its twofold reduction due to the exclusion of inappropriate (duplicate, unreliable, difficult to understand) items. In addition, the prior structure and conceptual framework have been remained in the intermediate PROM version. The next step is to analyze validity, reliability and sensitivity.

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**Conflicts of Interest:** nothing to declare.

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**Table 1**

## Summary of question selection according to the criteria of classical test theory and item response theory

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HTN_PHY_1** | 1,01 | 0,94 | 1,08 | 27,2 | 24,8 | 29,5 | -6,00 | 1,50 | 0,25 | 0,15 | 0,41 | 3 | 5 | ✓ | practical significance |
| **HTN_PHY_2** | 1,02 | 0,95 | 1,08 | 27,8 | 25,6 | 30,0 | -6,50 | 1,40 | 0,27 | 0,21 | 0,44 | 3 | 5 | ✓ | practical significance |
| **HTN_PHY_3** | 1,04 | 0,97 | 1,10 | 27,9 | 25,7 | 30,1 | -8,30 | 1,50 | 0,24 | 0,06 | 0,30 | 3 | 5 | ✓ | practical significance |
| **HTN_PHY_4** | 1,13 | 1,06 | 1,20 | 31,8 | 29,2 | 34,3 | -3,80 | 1,00 | 0,63 | 0,40 | 0,55 | 6 | 2 | ✓ | |
| HTN_PHY_5 | 1,21 | 1,11 | 1,30 | 32,6 | 29,1 | 36,0 | -4,50 | 0,72 | 0,39 | 0,32 | 0,30 | 4 | 4 | × | practical insignificance |
| HTN_PHY_6 | 0,68 | 0,57 | 0,77 | 14,8 | 12,3 | 17,1 | 0,90 | 0,72 | 0,46 | 0,20 | 0,44 | 1 | 7 | × | |
| **HTN_PHY_7** | 0,99 | 0,91 | 1,08 | 24,1 | 21,4 | 26,6 | -2,23 | 0,09 | 1,01 | 0,44 | 0,57 | 5 | 3 | ✓ | |
| **HTN_PHY_8** | 0,98 | 0,91 | 1,05 | 24,5 | 22,3 | 26,8 | -3,00 | 0,30 | 0,93 | 0,46 | 0,62 | 4 | 4 | ✓ | practical significance |
| **HTN_PHY_9** | 1,10 | 0,98 | 1,20 | 28,2 | 25,0 | 31,2 | -2,86 | 0,43 | 0,85 | 0,47 | 0,61 | 6 | 2 | ✓ | |
| **HTN_PHY_10** | 1,09 | 1,01 | 1,16 | 34,9 | 32,0 | 37,8 | -1,10 | 1,30 | 1,30 | 0,51 | 0,67 | 8 | 0 | ✓ | |
| **HTN_PHY_12** | 1,06 | 0,99 | 1,13 | 39,4 | 36,2 | 42,7 | 0,56 | 3,20 | 0,89 | 0,37 | 0,50 | 4 | 4 | ✓ | practical significance |
| HTN_PHY_13 | 0,94 | 0,85 | 1,03 | 23,7 | 21,1 | 26,3 | -1,90 | 0,70 | 0,33 | 0,30 | 0,41 | 3 | 5 | × | |
| HTN_PHY_14 | 0,91 | 0,85 | 0,97 | 24,4 | 22,6 | 26,2 | -4,60 | 1,14 | 0,36 | 0,29 | 0,35 | 2 | 6 | × | |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HTN_PSY_1** | 1,14 | 1,05 | 1,21 | 29,8 | 27,0 | 32,5 | -4,50 | -1,70 | 0,16 | 0,20 | 0,44 | 4 | 4 | ✓ | practical significance |
| HTN_PSY_2 | 1,42 | 1,35 | 1,49 | 42,5 | 39,1 | 45,9 | -2,52 | 2,80 | 0,08 | 0,20 | 0,74 | 2 | 6 | × | practical insignificance |
| **HTN_PSY_3** | 1,32 | 1,25 | 1,39 | 45,1 | 41,8 | 48,4 | -0,63 | 1,75 | 0,67 | 0,38 | 0,82 | 7 | 1 | ✓ | |
| **HTN_PSY_4** | 1,35 | 1,29 | 1,42 | 43,6 | 40,5 | 46,9 | -1,49 | 1,12 | 0,54 | 0,50 | 0,43 | 7 | 1 | ✓ | |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HTN_SOC_1 | 0,97 | 0,89 | 1,06 | 25,1 | 22,4 | 27,6 | -4,30 | 1,98 | 0,43 | 0,49 | 0,54 | 3 | 5 | × | |
| HTN_SOC_2 | 0,97 | 0,89 | 1,04 | 26,1 | 23,5 | 28,5 | -3,38 | 1,64 | 0,37 | 0,44 | 0,68 | 3 | 5 | × | |
| **HTN_SOC_3** | 0,90 | 0,81 | 0,98 | 22,6 | 20,0 | 25,0 | -4,14 | 1,40 | 0,37 | 0,36 | 0,55 | 3 | 5 | ✓ | practical significance |
| HTN_SOC_4 | 1,30 | 1,21 | 1,38 | 35,3 | 31,9 | 38,7 | -3,30 | 0,88 | 0,20 | 0,17 | 0,43 | 5 | 3 | × | practical insignificance |
| **HTN_SOC_5** | 1,11 | 1,03 | 1,18 | 29,7 | 27,0 | 32,3 | -1,36 | 0,57 | 2,58 | 0,50 | 0,66 | 8 | 0 | ✓ | |
| **HTN_SOC_7** | 1,03 | 0,96 | 1,11 | 30,0 | 27,4 | 32,6 | -1,29 | 1,06 | 2,99 | 0,52 | 0,68 | 6 | 2 | ✓ | |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HTN_THER_1** | 0,82 | 0,76 | 0,89 | 21,9 | 20,0 | 23,8 | -3,34 | 2,08 | 0,48 | 0,43 | 0,52 | 3 | 5 | ✓ | practical significance |
| **HTN_THER_2** | 0,90 | 0,79 | 0,99 | 21,5 | 18,7 | 24,2 | -4,14 | 0,08 | 0,18 | 0,14 | 0,65 | 2 | 6 | ✓ | practical significance |
| **HTN_THER_3** | 0,85 | 0,77 | 0,92 | 22,3 | 20,2 | 24,5 | -3,04 | 2,59 | 0,29 | 0,24 | 0,57 | 3 | 5 | ✓ | practical significance |
| **HTN_THER_4** | 1,05 | 0,92 | 1,15 | 24,7 | 21,3 | 27,9 | -1,55 | 3,66 | 0,19 | 0,24 | 0,71 | 4 | 4 | ✓ | practical significance |
| **HTN_THER_5** | 1,01 | 0,91 | 1,10 | 24,9 | 21,9 | 27,6 | -3,46 | -0,40 | 0,23 | 0,33 | 0,65 | 4 | 4 | ✓ | practical significance |
| HTN_THER_6 | 1,11 | 1,01 | 1,19 | 27,4 | 24,3 | 30,2 | -4,97 | -0,84 | 0,31 | 0,34 | 0,35 | 4 | 4 | × | practical insignificance |
| HTN_THER_7 | 0,96 | 0,88 | 1,03 | 24,0 | 21,7 | 26,2 | -5,85 | 0,64 | 0,46 | 0,39 | 0,43 | 2 | 6 | × | |
| HTN_THER_9 | 1,23 | 1,13 | 1,31 | 33,4 | 29,8 | 36,7 | -3,30 | 2,66 | 0,17 | 0,10 | 0,24 | 4 | 4 | × | practical insignificance |
| HTN_ THER_10 | 1,25 | 1,14 | 1,34 | 59,2 | 56,0 | 62,6 | 2,40 | 2,80 | 0,12 | 0,03 | 0,30 | 5 | 3 | × | practical insignificance |
| HTN_ THER_11 | 1,09 | 0,99 | 1,19 | 27,3 | 24,0 | 30,5 | -2,82 | -0,87 | 0,17 | 0,22 | 0,29 | 5 | 3 | × | practical insignificance |
| HTN_ THER_12 | 1,16 | 1,09 | 1,23 | 34,4 | 31,9 | 36,9 | -5,40 | 4,80 | 0,28 | 0,35 | 0,48 | 4 | 4 | × | practical insignificance |
| HTN_THER_13 | 1,02 | 0,93 | 1,10 | 26,5 | 23,8 | 29,1 | -5,37 | 1,64 | 0,19 | 0,13 | 0,45 | 3 | 5 | × | |
| HTN_THER_14 | 0,73 | 0,66 | **0,80** | 16,4 | 14,6 | 18,2 | -5,80 | 2,20 | 0,25 | 0,03 | 0,12 | 0 | 8 | × | |

**Abbreviations:** SD — standard deviation, CV — coefficient of variation, Pearson's r — Pearson's item-total correlation coefficient, CI — confidence interval, CBC_b1, CBC_b4 — the degree of question's difficulty (b1<b4).

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PHY_1_1 | 0,94 | 0,85 | 1,01 | 25,8 | 23,1 | 28,3 | -8 | 2,3 | 0,39 | 0,44 | 0,56 | 3 | 5 | × | |
| **PHY_1_2** | 1,03 | 0,92 | 1,12 | 26,5 | 23,3 | 29,7 | -3 | 0,2 | 0,75 | 0,59 | 0,67 | 7 | 1 | ✓ | |
| PHY_1_3 | 0,99 | 0,87 | 1,04 | 24,4 | 21,6 | 26,8 | -4,4 | -0,4 | 1,00 | 0,59 | 0,68 | 5 | 3 | × | discrepancy with the HTN concept |
| **PHY_1_4** | 0,99 | 0,91 | 1,06 | 24,5 | 22,0 | 26,8 | -4,1 | -0,8 | 1,18 | 0,64 | 0,73 | 5 | 3 | ✓ | |
| PHY_1_5 | 1,19 | 1,11 | 1,26 | 34,9 | 32,0 | 37,7 | -3 | 7,9 | 0,62 | 0,54 | 0,64 | 7 | 1 | × | discrepancy with the HTN concept |
| **PHY_1_6** | 1,17 | 1,05 | 1,23 | 30,4 | 26,8 | 33,1 | -1,9 | -0,4 | 0,60 | 0,54 | 0,62 | 8 | 0 | ✓ | |
| PHY_1_7 | 1,33 | 1,24 | 1,42 | 45 | 41 | 48 | -1,5 | 6,5 | 0,73 | 0,69 | 0,71 | 7 | 1 | × | discrepancy with the HTN concept |
| PHY_1_9 | 0,77 | 0,67 | 0,86 | 16,7 | 14,6 | 18,2 | -3,6 | 1,77 | 1,10 | 0,51 | 0,59 | 3 | 5 | × | |
| **PHY_1_10** | 1,15 | 1,03 | 1,25 | 29,0 | 25,4 | 32,5 | -2 | -0,72 | 0,86 | 0,63 | 0,70 | 8 | 0 | ✓ | |
| **PHY_1_11** | 1,21 | 1,12 | 1,27 | 31,9 | 29,1 | 34,7 | -3,4 | -0,6 | 0,72 | 0,61 | 0,63 | 7 | 1 | ✓ | |
| **PHY_1_13** | 1,15 | 1,06 | 1,23 | 32,3 | 29,0 | 35,5 | -2,5 | 0,56 | 0,65 | 0,53 | 0,62 | 8 | 0 | ✓ | |
| **PHY_1_16** | 1,10 | 1,02 | 1,18 | 27,2 | 23,6 | 30,4 | -2,3 | 0,6 | 0,79 | 0,54 | 0,62 | 8 | 0 | ✓ | |
| PHY_1_20 | 0,76 | 0,66 | 0,84 | 17,6 | 15,1 | 19,8 | -3,3 | -0,1 | 0,53 | 0,46 | 0,55 | 2 | 6 | × | |
| PHY_1_21 | 0,91 | 0,83 | 1,00 | 22,1 | 20,0 | 24,5 | -4,43 | -0,23 | 0,68 | 0,57 | 0,63 | 4 | 4 | × | |
| PHY_1_25 | 1,04 | 0,90 | 1,09 | 26,7 | 23,9 | 30,4 | -3,76 | -0,27 | 0,53 | 0,48 | 0,55 | 6 | 2 | × | low reliability |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PHY_2_1** | 1,07 | 0,98 | 1,15 | 32,0 | 29,1 | 35,0 | -2,6 | 1,47 | 0,89 | 0,69 | 0,80 | 7 | 1 | ✓ | |
| **PHY_2_2** | 1,10 | 1,02 | 1,18 | 35,0 | 32,1 | 38,15 | -3,20 | 2.0 | 0,60 | 0,61 | 0,82 | 7 | 1 | ✓ | |
| PHY_2_7 | 1,32 | 1,24 | 1,42 | 40,4 | 35,9 | 43,1 | -2,65 | 0,80 | 0,60 | 0,60 | 0,72 | 8 | 0 | ✓ | |
| PHY_2_9 | 0,90 | 0,82 | 0,99 | 22,0 | 20,0 | 25,0 | -6,10 | 0,01 | 0,47 | 0,46 | 0,59 | 3 | 5 | × | |
| PHY_2_10 | 1,03 | 0,95 | 1,11 | 31,0 | 28,1 | 33,9 | -5,05 | 4,60 | 0,24 | 0,37 | 0,59 | 4 | 4 | × | |
| PHY_2_12 | 0,97 | 0,84 | 1,07 | 24,1 | 21,3 | 26,3 | -4,54 | -0,16 | 0,60 | 0,51 | 0,62 | 4 | 4 | × | |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PHY_3_3** | 1,35 | 1,24 | 1,42 | 41,7 | 39,8 | 46,2 | -2,70 | 0,58 | 0,77 | 0,629 | 0,79 | 8 | 0 | ✓ | |
| PHY_3_4 | 1,05 | 0,97 | 1,14 | 34,5 | 31,6 | 37,5 | -2,63 | 0,99 | 1,11 | 0,657 | 0,82 | 7 | 1 | × | duplication of the HTN-specific part |
| **PHY_3_5** | 1,19 | 1,10 | 1,28 | 45,8 | 42,7 | 49,1 | -1,81 | 1,58 | 1,00 | 0,686 | 0,83 | 8 | 0 | ✓ | |
| PHY_3_6 | 1,03 | 0,95 | 1,11 | 36,2 | 32,7 | 39,5 | -2,30 | 2,45 | 0,72 | 0,567 | 0,76 | 7 | 1 | × | practical insignificance |
| **PHY_3_8** | 1,20 | 1,13 | 1,28 | 44,4 | 41,3 | 47,8 | -1,63 | 1,56 | 1,21 | 0,735 | 0,88 | 8 | 0 | ✓ | |

| Question | SD | Lower confi-dence limit | Upper confi-dence limit | Coefficient of variation | Lower confi-dence limit | Upper confi-dence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PHY_4_2** | 1,25 | 1,17 | 1,32 | 32,9 | 30,0 | 35,7 | -2,9 | -0,88 | 1,24 | 0,74 | 0,80 | 8 | 0 | ✓ | |
| PHY_4_3 | 1,18 | 1,10 | 1,26 | 32,1 | 29,0 | 34,9 | -2,73 | -0,7 | 1,11 | 0,65 | 0,72 | 8 | 0 | × | practical insignificance |
| PHY_4_4 | 1,07 | 0,96 | 1,16 | 25,4 | 22,2 | 28,3 | -2,47 | -2,19 | 1,00 | 0,62 | 0,70 | 7 | 1 | × | practical insignificance |
| PHY_4_5 | 1,22 | 1,11 | 1,32 | 30,9 | 27,2 | 34,2 | -2,26 | -1,58 | 0,94 | 0,63 | 0,71 | 8 | 0 | × | practical insignificance |
| **PHY_4_7** | 1,26 | 1,16 | 1,36 | 32,4 | 28,9 | 35,9 | -2,28 | -1,44 | 1,07 | 0,68 | 0,76 | 8 | 0 | ✓ | |
| PHY_4_8 | 1,20 | 1,10 | 1,29 | 30,0 | 26,5 | 33,2 | -2,47 | -1,6 | 1,14 | 0,69 | 0,78 | 8 | 0 | × | practical insignificance |
| **PHY_4_9** | 1,33 | 1,25 | 1,42 | 38,1 | 34,7 | 41,4 | -1,93 | -0,05 | 1,79 | 0,80 | 0,85 | 8 | 0 | ✓ | |
| PHY_4_10 | 1,32 | 1,24 | 1,39 | 40,1 | 36,8 | 43,3 | -2,14 | 0,626 | 1,40 | 0,78 | 0,82 | 8 | 0 | × | duplication |
| PHY_4_12 | 1,26 | 1,18 | 1,34 | 35,2 | 32,1 | 38,4 | -2,2 | 0,05 | 1,64 | 0,75 | 0,82 | 8 | 0 | × | duplication |
| **PHY_4_13** | 1,20 | 1,12 | 1,28 | 36,6 | 33,4 | 39,7 | -2,26 | 0,64 | 1,16 | 0,75 | 0,75 | 8 | 0 | ✓ | |
| PHY_4_14 | 1,22 | 1,14 | 1,28 | 33,2 | 30,6 | 36,0 | -2,41 | -0,17 | 1,85 | 0,80 | 0,84 | 8 | 0 | × | duplication of the HTN-specific part |
| PHY_4_15 | 0,80 | 0,65 | 0,83 | 17,1 | 14,8 | 20,0 | -4,67 | -3,09 | 0,75 | 0,42 | 0,54 | 2 | 6 | × | duplication of the HTN-specific part |
| PHY_4_17 | 1,17 | 1,07 | 1,27 | 29,2 | 25,7 | 32,4 | -2,3 | -0,8 | 2,00 | 0,73 | 0,81 | 8 | 0 | × | duplication of the HTN-specific part |
| **PHY_4_19** | 0,96 | 0,86 | 1,05 | 22,5 | 20,0 | 25,1 | -2,13 | -1.12 | 1,20 | 0,57 | 0,67 | 5 | 3 | ✓ | |
| **PHY_4_20** | 1,16 | 1,05 | 1,25 | 29,1 | 25,6 | 32,2 | -2,66 | -0,7 | 1,16 | 0,61 | 0,71 | 8 | 0 | ✓ | |

| Question | SD | Lower confi-dence limit | Upper confi-dence limit | Coefficient of variation | Lower confi-dence limit | Upper confi-dence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PHY_5_1 | 1,10 | 0,98 | 1,15 | 32,3 | 28,8 | 35,7 | -5,46 | 6,11 | 0,10 | 0,03 | 0,03 | 4 | 4 | × | |
| PHY_5_2 | 1,05 | 0,91 | 1,10 | 40,9 | 35,9 | 43,1 | -2,74 | 3,5 | 0,40 | 0,44 | 0,44 | 4 | 4 | × | |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PSY_1_1** | 1,12 | 1,03 | 1,21 | 34,5 | 31,1 | 37,8 | -3,10 | 1,68 | 0,68 | 0,61 | 0,75 | 7 | 1 | ✓ | |
| **PSY_1_2** | 1,02 | 0,91 | 1,11 | 24,4 | 21,2 | 27,4 | -3,87 | -0,76 | 0,80 | 0,61 | 0,75 | 6 | 2 | ✓ | |
| **PSY_1_3** | 1,07 | 0,97 | 1,16 | 27,5 | 24,1 | 30,7 | -4,48 | 0,17 | 0,78 | 0,65 | 0,73 | 6 | 2 | ✓ | |
| PSY_1_5 | 1,09 | 0,99 | 1,19 | 28,7 | 25,3 | 32,0 | -3,48 | 0,95 | 0,89 | 0,68 | 0,80 | 6 | 2 | × | practical insignificance |
| PSY_1_6 | 1,04 | 0,92 | 1,15 | 24,9 | 21,4 | 28,1 | -6,30 | -1,94 | 0,58 | 0,55 | 0,69 | 6 | 2 | × | practical insignificance |
| PSY_1_8 | 0,88 | 0,75 | 0,98 | 19,8 | 16,5 | 22,7 | -4,49 | -2,69 | 0,55 | 0,49 | 0,53 | 2 | 6 | × | |
| PSY_1_13 | 1,32 | 1,18 | 1,45 | 34,0 | 28,9 | 38,8 | -1,26 | -0,12 | 0,48 | 0,53 | 0,61 | 7 | 1 | × | practical insignificance |
| PSY_1_14 | 1,06 | 0,98 | 1,15 | 30,7 | 27,6 | 33,6 | -3,97 | 1,84 | 0,68 | 0,62 | 0,68 | 6 | 2 | × | practical insignificance |
| PSY_1_20 | 0,97 | 0,84 | 1,08 | 22,5 | 19,0 | 25,9 | -2,90 | -1,77 | 0,75 | 0,58 | 0,71 | 5 | 3 | × | practical insignificance |
| **PSY_1_23** | 1,07 | 0,96 | 1,17 | 27,1 | 23,6 | 30,4 | -4,14 | 0,05 | 0,98 | 0,67 | 0,78 | 6 | 2 | ✓ | |
| PSY_1_24 | 0,95 | 0,84 | 1,05 | 24,8 | 21,5 | 28,0 | -3,08 | 0,77 | 0,96 | 0,64 | 0,66 | 5 | 3 | × | practical insignificance |
| **PSY_1_25** | 1,05 | 0,94 | 1,15 | 27,7 | 24,1 | 31,2 | -3,07 | 0,58 | 0,99 | 0,69 | 0,77 | 6 | 2 | ✓ | |
| **PSY_1_28** | 1,09 | 1,00 | 1,17 | 28,7 | 25,6 | 31,7 | -3,84 | 0,40 | 1,21 | 0,75 | 0,75 | 7 | 1 | ✓ | |
| PSY_1_29 | 1,09 | 0,99 | 1,18 | 27,2 | 23,9 | 30,4 | -3,53 | -0,49 | 0,76 | 0,61 | 0,59 | 6 | 2 | × | practical insignificance |
| **PSY_1_30** | 1,26 | 1,15 | 1,35 | 35,2 | 31,3 | 39,1 | -2,31 | 0,32 | 0,92 | 0,70 | 0,63 | 8 | 0 | ✓ | |
| **PSY_1_33** | 1,16 | 1,05 | 1,26 | 30,5 | 26,7 | 34,1 | -2,66 | 0,19 | 1,36 | 0,78 | 0,86 | 8 | 0 | ✓ | |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PSY_2_1** | 1,08 | 0,99 | 1,17 | 31,6 | 28,2 | 34,9 | -3,10 | 1,85 | 0,95 | 0,66 | 0,85 | 6 | 2 | ✓ | |
| **PSY_2_2** | 1,13 | 1,05 | 1,21 | 32,4 | 29,4 | 35,3 | -3,48 | 0,43 | 1,01 | 0,70 | 0,88 | 7 | 1 | ✓ | |
| **PSY_2_5** | 1,04 | 0,95 | 1,13 | 28,3 | 25,0 | 31,5 | -2,99 | 0,65 | 1,44 | 0,76 | 0,89 | 7 | 1 | ✓ | |
| **PSY_2_7** | 1,13 | 1,04 | 1,21 | 30,8 | 27,7 | 33,8 | -3,31 | 0,33 | 1,52 | 0,78 | 0,87 | 7 | 1 | ✓ | |
| PSY_2_12 | 0,99 | 0,90 | 1,08 | 24,7 | 21,7 | 25,7 | -3,45 | -0,04 | 1,32 | 0,71 | 0,80 | 5 | 3 | × | practical insignificance |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PSY_4_2** | 1,09 | 1,01 | 1,17 | 31,8 | 28,8 | 34,7 | -2,90 | 1,42 | 1,33 | 0,74 | 0,81 | 8 | 0 | ✓ | |
| PSY_4_3 | 1,01 | 0,93 | 1,09 | 26,5 | 23,8 | 29,1 | -4,11 | 0,28 | 1,54 | 0,72 | 0,78 | 6 | 2 | × | practical insignificance |
| **PSY_4_5** | 1,10 | 1,01 | 1,19 | 32,8 | 29,7 | 36,0 | -2,59 | 1,53 | 1,51 | 0,74 | 0,79 | 8 | 0 | ✓ | |
| PSY_4_6 | 1,02 | 0,92 | 1,11 | 26,1 | 23,0 | 29,0 | -3,53 | 0,26 | 1,33 | 0,71 | 0,80 | 6 | 2 | × | practical insignificance |
| PSY_4_7 | 1,08 | 1,00 | 1,15 | 29,2 | 26,4 | 32,0 | -3,64 | 0,58 | 1,44 | 0,76 | 0,85 | 7 | 1 | × | practical insignificance |
| **PSY_4_8** | 1,01 | 0,92 | 1,09 | 25,6 | 22,8 | 28,2 | -4,08 | 0,10 | 1,48 | 0,72 | 0,81 | 6 | 2 | ✓ | |
| **PSY_4_9** | 1,08 | 1,00 | 1,16 | 30,9 | 28,1 | 33,6 | -3,33 | 1,21 | 1,56 | 0,75 | 0,80 | 7 | 1 | ✓ | |
| PSY_4_10 | 0,96 | 0,88 | 1,04 | 23,9 | 21,3 | 26,3 | -2,12 | 0,61 | 1,21 | 0,70 | 0,77 | 6 | 2 | × | practical insignificance |
| **PSY_4_11** | 1,07 | 0,96 | 1,17 | 26,9 | 23,3 | 30,3 | -3,17 | 0,03 | 1,19 | 0,68 | 0,78 | 6 | 2 | ✓ | |
| PSY_4_13 | 0,96 | 0,86 | 1,05 | 22,9 | 19,9 | 25,6 | -4,98 | -0,67 | 0,81 | 0,58 | 0,71 | 4 | 4 | × | |
| **PSY_4_14** | 1,04 | 0,93 | 1,14 | 25,6 | 22,2 | 28,9 | -4,03 | 0,42 | 0,78 | 0,59 | 0,77 | 6 | 2 | ✓ | |
| PSY_4_18 | 0,99 | 0,89 | 1,09 | 22,4 | 21,1 | 27,2 | -3,50 | -0,27 | 1,82 | 0,76 | 0,83 | 5 | 3 | × | |
| PSY_4_21 | 0,91 | 0,81 | 1,01 | 21,5 | 18,5 | 24,3 | -3,44 | -0,26 | 1,58 | 0,73 | 0,81 | 4 | 4 | × | |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PSY_5_4 | 0,94 | 0,85 | 1,03 | 34,3 | 30,8 | 37,8 | -5,59 | 3,82 | 0,33 | 0,34 | 0,92 | 3 | 5 | × | |
| **PSY_5_5** | 0,95 | 0,85 | 1,04 | 33,1 | 29,6 | 36,7 | -5,88 | 3,83 | 0,31 | 0,35 | 0,93 | 3 | 5 | ✓ | practical significance |
| **PSY_5_6** | 0,84 | 0,74 | 0,94 | 30,6 | 27,0 | 34,1 | -4,96 | 1,84 | 0,50 | 0,46 | 0,87 | 4 | 4 | ✓ | practical significance |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SOC_1_1** | 1,17 | 1,09 | 1,25 | 39,5 | 35,9 | 43,1 | -3,15 | 5,43 | 0,30 | 0,40 | 0,68 | 3 | 5 | ✓ | practical significance |
| SOC_1_2 | 0,85 | 0,75 | 0,95 | 20,4 | 17,5 | 23,1 | -0,80 | 0,34 | 0,86 | 0,52 | 0,63 | 4 | 4 | × | |
| SOC_1_7 | 1,08 | 0,98 | 1,17 | 29,2 | 25,7 | 32,6 | -3,04 | 1,73 | 0,75 | 0,60 | 0,72 | 6 | 2 | × | practical insignificance |
| **SOC_1_8** | 1,14 | 1,06 | 1,23 | 33,8 | 30,3 | 37,2 | -2,30 | 1,91 | 0,82 | 0,65 | 0,81 | 8 | 0 | ✓ | |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SOC_2_1 | 0,77 | 0,65 | 0,88 | 17,6 | 14,7 | 20,6 | -3,69 | 0,35 | 0,83 | 0,43 | 0,67 | 2 | 6 | × | |
| **SOC_2_3** | 0,91 | 0,82 | 0,98 | 21,9 | 19,4 | 24,2 | -1,92 | 0,42 | 1,08 | 0,60 | 0,76 | 5 | 3 | ✓ | |
| **SOC_2_5** | 0,90 | 0,82 | 0,97 | 23,3 | 20,8 | 25,7 | -3,75 | 1,27 | 1,08 | 0,58 | 0,75 | 5 | 3 | ✓ | |
| **SOC_2_8** | 0,90 | 0,79 | 0,99 | 21,2 | 18,3 | 23,9 | -1,10 | 0,08 | 1,19 | 0,56 | 0,76 | 5 | 3 | ✓ | |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SOC_3_1 | 0,85 | 0,76 | 0,94 | 20,9 | 18,2 | 23,5 | -4,00 | 1,07 | 0,89 | 0,53 | 0,66 | 3 | 5 | × | |
| **SOC_3_3** | 1,06 | 0,96 | 1,16 | 28,0 | 24,6 | 31,3 | -2,75 | 1,33 | 0,74 | 0,57 | 0,71 | 7 | 1 | ✓ | |
| SOC_3_4 | 0,87 | 0,78 | 0,96 | 22,4 | 19,7 | 24,9 | -3,31 | 1,72 | 0,60 | 0,42 | 0,65 | 3 | 5 | × | |
| SOC_3_5 | 0,82 | 0,70 | 0,92 | 19,2 | 16,1 | 22,1 | -2,67 | 0,25 | 0,80 | 0,50 | 0,62 | 4 | 4 | × | |
| SOC_3_7 | 0,99 | 0,86 | 1,11 | 23,8 | 20,0 | 27,3 | -3,80 | -0,05 | 0,49 | 0,42 | 0,50 | 2 | 6 | × | |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SOC_4_1 | 0,99 | 0,92 | 1,07 | 26,0 | 23,6 | 28,3 | -6,43 | 0,27 | 0,52 | 0,51 | 0,96 | 5 | 3 | × | duplication of the HTN-specific part |
| SOC_4_2 | 0,98 | 0,90 | 1,04 | 24,9 | 22,4 | 27,0 | -2,12 | 0,26 | 0,65 | 0,55 | 0,96 | 6 | 2 | × | duplication of the HTN-specific part |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **THER_1_1** | 0,77 | 0,67 | 0,92 | 20 | 16 | 23 | -2,1 | 0,5 | 1,7 | 0,57 | 0,82 | 5 | 3 | ✓ | |
| THER_1_2 | 0,72 | 0,68 | 0,85 | 20 | 17 | 22 | -2,8 | 0,9 | 1,5 | 0,57 | 0,85 | 5 | 3 | × | duplication of the HTN-specific part |
| THER_1_3 | 0,58 | 0,61 | 0,80 | 16 | 14 | 19 | -2,0 | 0,0 | 2,3 | 0,61 | 0,82 | 4 | 4 | × | duplication of the HTN-specific part |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **THER_2_1** | 0,88 | 0,78 | 0,99 | 25 | 21 | 28 | -3,10 | 1,80 | 0,80 | 0,47 | 0,70 | 4 | 4 | ✓ | practical significance |
| **THER_2_2** | 0,78 | 0,68 | 0,91 | 21 | 17 | 24 | -1,10 | 1,43 | 1,13 | 0,52 | 0,65 | 5 | 3 | ✓ | |
| **THER_2_3** | 1,01 | 0,82 | 1,04 | 25 | 22 | 29 | -3,90 | 1,50 | 0,74 | 0,54 | 0,63 | 7 | 1 | ✓ | |
| THER_2_7 | 0,78 | 0,59 | 0,90 | 25,1 | 19,3 | 30,1 | -2,45 | 3,10 | 0,45 | 0,35 | 0,56 | 2 | 6 | × | |

| Question | SD | Lower confidence limit | Upper confi-dence limit | Coefficient of variation | Lower confi-dence limit | Upper confi-dence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **THER_3_1** | 0,65 | 0,56 | 0,74 | 19,1 | 16,7 | 21,4 | -2,60 | 2,60 | 1,35 | 0,51 | 0,82 | 4 | 4 | ✓ | practical significance |
| THER_3_2 | 0,65 | 0,49 | 0,70 | 19,1 | 16,0 | 22,1 | -5,00 | 4,80 | 0,48 | 0,33 | 0,76 | 1 | 7 | × | |
| THER_3_4 | 0,70 | 0,63 | 0,86 | 22,2 | 18,3 | 25,6 | -0,67 | 3,08 | 0,81 | 0,41 | 0,84 | 3 | 5 | × | practical significance |

| Question | SD | Lower confidence limit | Upper confi-dence limit | Coefficient of variation | Lower confi-dence limit | Upper confi-dence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **THER_5_1** | 0,89 | 0,79 | 0,98 | 22,3 | 19,5 | 25,3 | -2,14 | 0,57 | 1,12 | 0,58 | 0,61 | 5 | 3 | ✓ | |
| **THER_5_2** | 0,73 | 0,63 | 0,83 | 18,2 | 15,3 | 20,8 | -2,11 | 0,87 | 1,89 | 0,67 | 0,67 | 4 | 4 | ✓ | practical significance |
| **THER_5_3** | 0,79 | 0,63 | 0,93 | 18,8 | 14,7 | 22,6 | -2,35 | -0,04 | 1,81 | 0,69 | 0,66 | 4 | 4 | ✓ | practical significance |
| THER_5_5 | 1,09 | 0,97 | 1,20 | 30 | 26 | 34 | -4,80 | 0,73 | 0,62 | 0,57 | 0,60 | 6 | 2 | × | practical insignificance |
| **THER_5_6** | 0,95 | 0,84 | 1,05 | 23,3 | 19,9 | 26,4 | -1,64 | -0,50 | 0,72 | 0,51 | 0,62 | 5 | 3 | ✓ | |
| **THER_5_7** | 1,06 | 0,93 | 1,17 | 27,0 | 22,8 | 30,8 | -4,76 | -0,27 | 0,54 | 0,47 | 0,55 | 5 | 3 | ✓ | |

| Question | SD | Lower confidence limit | Upper confi-dence limit | Coefficient of variation | Lower confi-dence limit | Upper confi-dence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| THER_6_1 | 0,63 | 0,54 | 0,72 | 15,0 | 12,6 | 17,3 | -4,60 | 1,45 | 0,45 | 0,37 | 0,58 | 1 | 7 | × | |
| THER_6_2 | 0,78 | 0,64 | 0,91 | 20 | 16 | 23 | -5,67 | 3,37 | 0,29 | 0,33 | 0,46 | 1 | 7 | × | |
| THER_6_3 | 0,79 | 0,63 | 0,93 | 19 | 14 | 22 | -4,65 | 0,34 | 0,35 | 0,34 | 0,52 | 1 | 7 | × | |
| THER_6_4 | 0,95 | 0,76 | 1,11 | 23 | 18 | 28 | -1,60 | -0,05 | 0,47 | 0,43 | 0,65 | 3 | 5 | × | |
| **THER_6_6** | 0,70 | 0,55 | 0,81 | 15 | 12 | 18 | -2,08 | -0,98 | 0,92 | 0,54 | 0,57 | 4 | 4 | ✓ | practical significance |
| THER_6_7 | 0,77 | 0,63 | 0,90 | 17 | 14 | 21 | -6,90 | -0,23 | 0,35 | 0,32 | 0,42 | 0 | 8 | × | |
| THER_6_8 | 0,85 | 0,66 | 1,02 | 19,1 | 14,2 | 23,3 | -8,30 | -5,27 | 0,16 | 0,33 | 0,59 | 1 | 7 | × | |

| Question | SD | Lower confidence limit | Upper confi-dence limit | Coefficient of variation | Lower confi-dence limit | Upper confi-dence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| THER_7_1 | 0,71 | 0,60 | 0,80 | 16,1 | 13,2 | 18,4 | -6,70 | -1,17 | 0,31 | 0,29 | 0,34 | 0 | 8 | × | |
| **THER_7_2** | 1,17 | 1,07 | 1,28 | 34,7 | 30,6 | 38,8 | -6,26 | 1,65 | 0,39 | 0,53 | 0,78 | 6 | 2 | ✓ | |
| **THER_7_3** | 1,09 | 0,97 | 1,21 | 31,9 | 27,4 | 36,3 | -5,55 | 2,85 | 0,39 | 0,50 | 0,80 | 5 | 3 | ✓ | |
| THER_7_5 | 1,19 | 1,01 | 1,33 | 31,1 | 25,2 | 36,3 | -4,47 | 0,23 | 0,14 | 0,22 | 0,57 | 5 | 3 | × | practical insignificance |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HTN_ PHY_1** | 1,01 | 0,94 | 1,08 | 27,2 | 24,8 | 29,5 | -6,00 | 1,50 | 0,25 | 0,15 | 0,41 | 3 | 5 | ✓ | practical significance |
| **HTN_ PHY_2** | 1,02 | 0,95 | 1,08 | 27,8 | 25,6 | 30,0 | -6,50 | 1,40 | 0,27 | 0,21 | 0,44 | 3 | 5 | ✓ | practical significance |
| **HTN_ PHY_3** | 1,04 | 0,97 | 1,10 | 27,9 | 25,7 | 30,1 | -8,30 | 1,50 | 0,24 | 0,06 | 0,30 | 3 | 5 | ✓ | practical significance |
| **HTN_ PHY_4** | 1,13 | 1,06 | 1,20 | 31,8 | 29,2 | 34,3 | -3,80 | 1,00 | 0,63 | 0,40 | 0,55 | 6 | 2 | ✓ | |
| HTN_PHY_5 | 1,21 | 1,11 | 1,30 | 32,6 | 29,1 | 36,0 | -4,50 | 0,72 | 0,39 | 0,32 | 0,30 | 4 | 4 | × | practical insignificance |
| HTN_PHY_6 | 0,68 | 0,57 | 0,77 | 14,8 | 12,3 | 17,1 | 0,90 | 0,72 | 0,46 | 0,20 | 0,44 | 1 | 7 | × | |
| **HTN_ PHY_7** | 0,99 | 0,91 | 1,08 | 24,1 | 21,4 | 26,6 | -2,23 | 0,09 | 1,01 | 0,44 | 0,57 | 5 | 3 | ✓ | |
| **HTN_ PHY_8** | 0,98 | 0,91 | 1,05 | 24,5 | 22,3 | 26,8 | -3,00 | 0,30 | 0,93 | 0,46 | 0,62 | 4 | 4 | ✓ | practical significance |
| **HTN_ PHY_9** | 1,10 | 0,98 | 1,20 | 28,2 | 25,0 | 31,2 | -2,86 | 0,43 | 0,85 | 0,47 | 0,61 | 6 | 2 | ✓ | |
| **HTN_ PHY_10** | 1,09 | 1,01 | 1,16 | 34,9 | 32,0 | 37,8 | -1,10 | 1,30 | 1,30 | 0,51 | 0,67 | 8 | 0 | ✓ | |
| **HTN_ PHY_12** | 1,06 | 0,99 | 1,13 | 39,4 | 36,2 | 42,7 | 0,56 | 3,20 | 0,89 | 0,37 | 0,50 | 4 | 4 | ✓ | practical significance |
| HTN_ PHY_13 | 0,94 | 0,85 | 1,03 | 23,7 | 21,1 | 26,3 | -1,90 | 0,70 | 0,33 | 0,30 | 0,41 | 3 | 5 | × | |
| HTN_ PHY_14 | 0,91 | 0,85 | 0,97 | 24,4 | 22,6 | 26,2 | -4,60 | 1,14 | 0,36 | 0,29 | 0,35 | 2 | 6 | × | |

| Question | SD | Lower confidence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confidence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HTN_ PSY_1** | 1,14 | 1,05 | 1,21 | 29,8 | 27,0 | 32,5 | -4,50 | -1,70 | 0,16 | 0,20 | 0,44 | 4 | 4 | ✓ | practical significance |
| HTN_PSY_2 | 1,42 | 1,35 | 1,49 | 42,5 | 39,1 | 45,9 | -2,52 | 2,80 | 0,08 | 0,20 | 0,74 | 2 | 6 | × | practical insignificance |
| **HTN_ PSY_3** | 1,32 | 1,25 | 1,39 | 45,1 | 41,8 | 48,4 | -0,63 | 1,75 | 0,67 | 0,38 | 0,82 | 7 | 1 | ✓ | |
| **HTN_ PSY_4** | 1,35 | 1,29 | 1,42 | 43,6 | 40,5 | 46,9 | -1,49 | 1,12 | 0,54 | 0,50 | 0,43 | 7 | 1 | ✓ | |

| Question | SD | Lower confi-dence limit | Upper confidence limit | Coefficient of variation | Lower confidence limit | Upper confi-dence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HTN_SOC_1 | 0,97 | 0,89 | 1,06 | 25,1 | 22,4 | 27,6 | -4,30 | 1,98 | 0,43 | 0,49 | 0,54 | 3 | 5 | × | |
| HTN_SOC_2 | 0,97 | 0,89 | 1,04 | 26,1 | 23,5 | 28,5 | -3,38 | 1,64 | 0,37 | 0,44 | 0,68 | 3 | 5 | × | |
| **HTN_ SOC_3** | 0,90 | 0,81 | 0,98 | 22,6 | 20,0 | 25,0 | -4,14 | 1,40 | 0,37 | 0,36 | 0,55 | 3 | 5 | ✓ | practical significance |
| HTN_SOC_4 | 1,30 | 1,21 | 1,38 | 35,3 | 31,9 | 38,7 | -3,30 | 0,88 | 0,20 | 0,17 | 0,43 | 5 | 3 | × | practical insignificance |
| HTN_SOC_5 | 1,11 | 1,03 | 1,18 | 29,7 | 27,0 | 32,3 | -1,36 | 0,57 | 2,58 | 0,50 | 0,66 | 8 | 0 | ✓ | |
| **HTN_ SOC_7** | 1,03 | 0,96 | 1,11 | 30,0 | 27,4 | 32,6 | -1,29 | 1,06 | 2,99 | 0,52 | 0,68 | 6 | 2 | ✓ | |

| Question | SD | Lower confi-dence limit | Upper confi-dence limit | Coefficient of variation | Lower confi-dence limit | Upper confi-dence limit | TT3_b1 | TT3_b4 | TT3_ discriminant_A | Cronbach's α | Pearson's r | Met the criteria | Did not meet the criteria | Selected | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HTN_ THER_1** | 0,82 | 0,76 | 0,89 | 21,9 | 20,0 | 23,8 | -3,34 | 2,08 | 0,48 | 0,43 | 0,52 | 3 | 5 | ✓ | practical significance |
| **HTN_ THER_2** | 0,90 | 0,79 | 0,99 | 21,5 | 18,7 | 24,2 | -4,14 | 0,08 | 0,18 | 0,14 | 0,65 | 2 | 6 | ✓ | practical significance |
| **HTN_ THER_3** | 0,85 | 0,77 | 0,92 | 22,3 | 20,2 | 24,5 | -3,04 | 2,59 | 0,29 | 0,24 | 0,57 | 3 | 5 | ✓ | practical significance |
| **HTN_ THER_4** | 1,05 | 0,92 | 1,15 | 24,7 | 21,3 | 27,9 | -1,55 | 3,66 | 0,19 | 0,24 | 0,71 | 4 | 4 | ✓ | practical significance |
| **HTN_ THER_5** | 1,01 | 0,91 | 1,10 | 24,9 | 21,9 | 27,6 | -3,46 | -0,40 | 0,23 | 0,33 | 0,65 | 4 | 4 | ✓ | practical significance |
| HTN_ THER_6 | 1,11 | 1,01 | 1,19 | 27,4 | 24,3 | 30,2 | -4,97 | -0,84 | 0,31 | 0,34 | 0,35 | 4 | 4 | × | practical insignificance |
| HTN_ THER_7 | 0,96 | 0,88 | 1,03 | 24,0 | 21,7 | 26,2 | -5,85 | 0,64 | 0,46 | 0,39 | 0,43 | 2 | 6 | × | |
| HTN_ THER_9 | 1,23 | 1,13 | 1,31 | 33,4 | 29,8 | 36,7 | -3,30 | 2,66 | 0,17 | 0,10 | 0,24 | 4 | 4 | × | practical insignificance |
| HTN_ THER_10 | 1,25 | 1,14 | 1,34 | 59,2 | 56,0 | 62,6 | 2,40 | 2,80 | 0,12 | 0,03 | 0,30 | 5 | 3 | × | practical insignificance |
| HTN_ THER_11 | 1,09 | 0,99 | 1,19 | 27,3 | 24,0 | 30,5 | -2,82 | -0,87 | 0,17 | 0,22 | 0,29 | 5 | 3 | × | practical insignificance |
| HTN_ THER_12 | 1,16 | 1,09 | 1,23 | 34,4 | 31,9 | 36,9 | -5,40 | 4,80 | 0,28 | 0,35 | 0,48 | 4 | 4 | × | practical insignificance |
| HTN_ THER_13 | 1,02 | 0,93 | 1,10 | 26,5 | 23,8 | 29,1 | -5,37 | 1,64 | 0,19 | 0,13 | 0,45 | 3 | 5 | × | |
| HTN_ THER_14 | 0,73 | 0,66 | 0,80 | 16,4 | 14,6 | 18,2 | -5,80 | 2,20 | 0,25 | 0,03 | 0,12 | 0 | 8 | × | |

# Health-related Quality-of-Life Questionnaire for Patients with Hypertension

Please answer questions regarding your general state, mood and treatment. Your answers will help your doctor work to improve th e quality of care. Answer each question by marking the answer you have chosen as stated. If you are not sure how to answer the question, please choose the answer that most accurately reflects your view.

COMBINED_PHY

| How often OVER THE LAST 4 WEEKS have you noticed the following disorders? | | | | | | |
|---|---|---|---|---|---|---|
| | | 5 | 4 | 3 | 2 | 1 |
| HTN_PHY_1 | Ripple in the head | Never | Rarely | At times | Often | Permanently |
| HTN_PHY_2 | Dull pressing or aching pain in the back or other part of the head | Never | Rarely | At times | Often | Permanently |
| HTN_PHY_3 | Rush of blood, fever sensation | Never | Rarely | At times | Often | Permanently |
| HTN_PHY_4 | Muscae volitantes, visual snow | Never | Rarely | At times | Often | Permanently |
| HTN_PHY_7 | Nausea with pressure increase | Never | Rarely | At times | Often | Permanently |
| HTN_PHY_8 | Feeling of pressure on the head | Never | Rarely | At times | Often | Permanently |
| HTN_PHY_9 | Trembling in the arms and/or legs | Never | Rarely | At times | Often | Permanently |
| HTN_PHY_10 | How worried were you of the symptoms of high blood pressure? | Did not worry | A bit | Moderately | Highly | Very worried |
| HTN_PHY_12 | How often have you noticed high blood pressure? | Never | Very rarely (1-2 times a month) | At times (1-2 times a week) | More than 3 times a week | Every day |
| PHY 1_2 | Vertigo | Never | Rarely | At times | Often | Permanently |
| PHY 1_4 | Ttightness in the chest | Never | Rarely | At times | Often | Permanently |
| PHY 1_6 | Numbness in limbs | Never | Rarely | At times | Often | Permanently |
| PHY 1_10 | Swelling of the legs | Never | Rarely | At times | Often | Permanently |
| PHY 1_11 | Frequent night urination | Never | Rarely | At times | Often | Permanently |
| PHY 1_13 | Increased sweating | Never | Rarely | At times | Often | Permanently |
| PHY 1_16 | Sudden turbidity, blurriness, grey-out | Never | Rarely | At times | Often | Permanently |

| How often OVER THE LAST 4 WEEKS have you noted the following disorders? | | | | | | |
|---|---|---|---|---|---|---|
| | | 5 | 4 | 3 | 2 | 1 |
| PHY 2_1 | Poor general state | Never | Rarely | At times | Often | Permanently |
| PHY 2_2 | Weakness, lethargy | Never | Rarely | At times | Often | Permanently |
| PHY 2_7 | Frequent night awakenings | Never | Rarely | At times | Often | Permanently |

| Please answer the following questions about your health status now. | | | | | | |
|---|---|---|---|---|---|---|
| | | 5 | 4 | 3 | 2 | 1 |
| PHY 3_3 | Do you feel anxiety or depression because of your health? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |
| | | 1 | 2 | 3 | 4 | 5 |
| PHY 3_5 | Are you satisfied with your physical condition, performance? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |
| PHY 3_8 | Do you feel healthy? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |
| To what extent has your physical and general state limited you in the following activities OVER THE LAST 4 WEEKS? | | | | | | |
| | | 5 | 4 | 3 | 2 | 1 |
| PHY 4_2 | Lift and/or carry a bag of groceries, weights | Not at al | A bit | Moderately | Rather | Extremely |
| PHY 4_7 | Walk a few blocks | Not at al | A bit | Moderately | Rather | Extremely |
| Did your physical condition affect your daily activities IN THE LAST 4 WEEKS in such a way that: | | | | | | |
| | | 5 | 4 | 3 | 2 | 1 |
| PHY 4_9 | I had to reduce the amount of time spent on work or other matters | Never | Rarely | At times | Often | Permanently |
| PHY 4_13 | Doing work required extra effort or extra time | Never | Rarely | At times | Often | Permanently |
| OVER THE LAST 4 WEEKS, to what extent did your physical condition limit you in the following activities: | | | | | | |
| | | 5 | 4 | 3 | 2 | 1 |
| PHY 4_19 | In your favorite activities | Not at al | A bit | Moderately | Rather | Extremely |
| PHY 4_20 | In intimate life | Not at al | A bit | Moderately | Rather | Extremely |

## COMBINED_PSY

| How often OVER THE LAST 4 WEEKS have you noted the following emotional states? | | | | | | |
|---|---|---|---|---|---|---|
| | | 5 | 4 | 3 | 2 | 1 |
| PSY 1_1 | Anxiety, emotional stress | Never | Rarely | At times | Often | Permanently |
| PSY 1_2 | Sudden and baseless scare | Never | Rarely | At times | Often | Permanently |
| PSY 1_3 | Tearfulness , low mood | Never | Rarely | At times | Often | Permanently |
| PSY 1_23 | Frequent and baseless change in sentiment | Never | Rarely | At times | Often | Permanently |
| PSY 1_25 | Constant anxiety | Never | Rarely | At times | Often | Permanently |
| PSY 1_28 | Loss of pleasure from what used to afford it | Never | Rarely | At times | Often | Permanently |
| PSY 1_30 | Feeling that you do everything very slowly | Never | Rarely | At times | Often | Permanently |
| PSY 1_33 | Feeling of burnout | Never | Rarely | At times | Often | Permanently |

| How often OVER THE LAST 4 WEEKS have you noted the following manifestations? | | | | | | |
|---|---|---|---|---|---|---|
| | | 5 | 4 | 3 | 2 | 1 |
| PSY 2_1 | Forgetfulness | Never | Rarely | At times | Often | Permanently |
| PSY 2_2 | Difficulties remembering a new | Never | Rarely | At times | Often | Permanently |
| PSY 2_5 | Distraction, difficulty in focusing | Never | Rarely | At times | Often | Permanently |
| PSY 2_7 | Feeling that you began to think slower | Never | Rarely | At times | Often | Permanently |
| Please answer the following questions about how you satisfy with yourself and life now. | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 |
| PSY 3_2 | Do you feel that your life is meaningful? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |
| PSY 3_9 | Do you feel that you are managing the events of your own life? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |

| OVER THE LAST 4 WEEKS, how often your emotional state influenced your daily activities in such a way that: | | | | | | |
|---|---|---|---|---|---|---|
| | | 5 | 4 | 3 | 2 | 1 |
| PSY 4_2 | Completed less than desirable | Never | Rarely | At times | Often | Permanently |
| PSY 4_5 | Doing work required extra effort or extra time | Never | Rarely | At times | Often | Permanently |
| OVER THE LAST 4 WEEKS, did it happen that problems with memory, attention concentration or fast mental fatigue influenced your daily activities in such a way that: | | | | | | |
| | | 5 | 4 | 3 | 2 | 1 |
| PSY 4_8 | Did not do job or other tasks as accurately as usual | Never | Rarely | At times | Often | Permanently |
| PSY 4_9 | Doing work required extra effort or extra time | Never | Rarely | At times | Often | Permanently |
| FOR THE LAST 4 WEEKS, to what extent did your emotional state limit you in the following activities: | | | | | | |
| | | 5 | 4 | 3 | 2 | 1 |
| PSY 4_11 | In work (in professional activities, training or household chores) | Not at all | A bit | Moderately | Rather | Very much |
| PSY 4_14 | In your hobby, favorite activities | Not at all | A bit | Moderately | Rather | Very much |

| Please answer the following questions about how you evaluate the change in your mood and mental performance. | | | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 |
| PSY 5_5 | How do you assess your satisfaction with yourself and life now compared to year earlier? | Significantly worse | A bit worse | No change | A bit better | Significantly better |
| PSY 5_6 | How do you assesse your memory, attention and mental performance now compared to year earlier? | Significantly worse | A bit worse | No change | A bit better | Significantly better |

| Please answer how relevant the following statements consist to your point of view. | | | | | | |
|---|---|---|---|---|---|---|
| a. | | 1 | 2 | 3 | 4 | 5 |
| HTN_PSY_1 | Believe that I am healthy, and high blood pressure is not a disease and cannot be a cause for worry | Certainly yes | Probably yes | Tough to tell | Probably not | Certainly not |
| b. | | 1 | 2 | 3 | 4 | 5 |
| HTN_PSY_3 | I constantly think about how to fight against with hypertension (high blood pressure) | Certainly yes | Probably yes | Tough to tell | Probably not | Certainly not |
| HTN_PSY_4 | I am depressed and worried by the idea that the treatment of hypertension (high blood pressure) should be constantly carried out | Certainly yes | Probably yes | Tough to tell | Probably not | Certainly not |

## COMBINED_SOC

| Please note how satisfied you are currently with... | | | | | | |
|---|---|---|---|---|---|---|
| | | 5 | 4 | 3 | 2 | 1 |
| SOC 1_1 | ... your financial situation | Completely satisfied | Rather satisfied | Tough to tell | Rather not satisfied | Completely not satisfied |
| SOC 1_8 | ... recreational opportunities | Completely satisfied | Rather satisfied | Tough to tell | Rather not satisfied | Completely not satisfied |

| Please answer the questions regarding your social environment. | | | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 |
| SOC 2_3 | Do you always have the opportunity to get the information you need in everyday life? | Never | Rarely | At times | Often | Permanently |
| SOC 2_5 | Do you often get information for everyday life from your friends, relatives (for example, about a good doctor, interesting film, etc.)? | Never | Rarely | At times | Often | Permanently |
| SOC 2_8 | Do you feel that there are enough people around with whom you have a good relationship? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |

| a. **Please answer the questions regarding medical care availability for you.** | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| SOC 3_3 | Is the medical care you need available for you? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |
| HTN_SOC_3 | Are you satisfied with how your doctor treats hypertension (high blood pressure)? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |
| Please mark the appropriate answer describing the situation FOR THE LAST 4 WEEKS? | | | | | | |
| b. | | 5 | 4 | 3 | 2 | 1 |
| HTN_SOC_5 | How often did the pressure increase interfere you continuing a normal family, friendly conversation, or professional? | Never | Rarely | At times | Often | Very Often |
| HTN_SOC_7 | How often did you have to put off your household or referral tasks for a while to tackle the blood pressure increase? | Never | Rarely | At times | Often | Very Often |

COMBINED_THER

| a. Please answer the following questions regarding your satisfaction with the treatment. | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| THER 1_1 | Are you satisfied with the treatment? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |
| HTN_THER_1 | In your opinion, is the treatment of hypertension (high blood pressure) prescribed for you effective now? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |
| HTN_THER_2 | In your opinion, is the treatment of hypertension (high blood pressure) prescribed for you required now? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |
| | | 1 | 2 | 3 | 4 | 5 |
| THER 2_1 | How has your performance changed during/after treatment? | Significantly worsened | Worsened a bit | No change | Improved a bit | Significantly improved |
| THER 2_2 | How has your general state changed during/after treatment? | Significantly worsened | Worsened a bit | No change | Improved a bit | Significantly improved |
| THER 2_3 | The number and intensity of the symptoms during/after treatment… | Significantly increased | Increased a bit | No change | Decreased a bit | Significantly decreased |

| | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| THER 3_1 | How has your usual emotional state changed during/after treatment? | Significantly worsened | Worsened a bit | No change | Improved a bit | Significantly improved |
| | | 5 | 4 | 3 | 2 | 1 |
| THER 5_1 | Do you find the regimen of your prescribed medication too complicated? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |
| THER 5_2 | Do you find the doctor's recommendations for lifestyle changing too complicated? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |
| THER 5_3 | How difficult is it for you to follow the doctor's recommendations regarding medication and lifestyle changes? | Certainly easy | Rather easy | Tough to tell | Rather difficult | Very difficult |
| THER 5_6 | How often do you have side effects from medications prescribed by your doctor? | Never | Rarely | At times | Often | Permanently |
| THER 5_7 | How worried are you about the side effects of prescribed medications? | Do not worry | A bit | Moderately | Much | Extremely |
| b. | | 5 | 4 | 3 | 2 | 1 |
| HTN_THER_3 | How often do you keep from buying antihypertensive drugs prescribed by your doctor? | Never | Rarely | At times | Often | Permanently |
| HTN_THER_4 | How often have you missed taking antihypertensive drugs due to fear of side effects? | Never | Rarely | At times | Often | Very often |
| HTN_THER_5 | Can you independently replace the medications prescribed by your doctor? | Certainly not | Probably not | Tough to tell | Probably yes | Certainly yes |
| THER 6_6 | How often do you independently change the dosage of the prescribed medicine? | Never | Rarely | At times | Often | Permanently |
| THER 7_2 | Do you follow the doctor's recommendations regarding physical activity and exercise? | Yes always | Usually yes | At times | Rarely и selectively | No, never |
| THER 7_3 | Do you follow the doctor's recommendations regarding the diet regimen and composition? | Yes always | Usually yes | At times | Rarely и selectively | No, never |

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# Prediction of antiarrhythmic therapy effectiveness in children

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**Aim.** To optimize treatment tactics in children with arrhythmias based on the evaluation and prediction of the therapy efficacy.

**Material and methods.** Prospective cohort study was performed from 2007 to 2017. A total of 100 patients aged 0 to 7 years with different types of significant arrhythmias received prophylactic antiarrhythmic therapy. Data of medical history, 12-lead electrocardiography (ECG), Holter ECG monitoring, and echocardiography were studied. To verify electrophysiological variant of tachycardia, some patients underwent transesophageal electrophysiologic study.

**Results.** The study showed that antiarrhythmic drug therapy was most efficacious in patients till one year old without signs of arrhythmogenic cardiomyopathy (ACM). Older age of children, the presence of pronounced ACM manifestations are factors that increase the risk of ineffective AAT. Based on the data obtained, a multifactor model was developed to predict the effectiveness of prolonged antiarrhythmic therapy.

**Conclusion.** The study showed that age and intracardiac hemodynamic status affected the efficacy of antiarrhythmic therapy. Proposed model allowed to avoid unnecessary prolonged pharmacological load and to timely administer other methods of treatment in case when ineffective result of the antiarrhythmic therapy was predicted.

**Key words:** children, arrhythmia, arrhythmogenic cardiomyopathy, prediction model, prolonged antiarrhythmic therapy.

**Conflicts of Interest:** nothing to declare.

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Pediatric arrhythmology remains one of the most controversial areas in pediatric cardiology. An open question there, first of all, regards patients of the first years of life. Preventive antiarrhythmic therapy is used mainly in early childhood, firstly, due to the high chance of spontaneous resolution of tachycardia and, secondly, because of higher indications for radiofrequency ablation (RFA) in this age group. It should be remembered that antiarrhythmic therapy is not a definitive method in tachyarrhythmia treatment in children, but only helps them "outgrow" arrhythmia. So, the aim of this is to control the rhythm up to 1-1,5 years, when in most children there is a spontaneous remission of tachycardia due to completing of heart development. After the first year of life, the probability of spontaneous tachycardia resolution is significantly reduced [1]. Data on drug resistance, deaths, and life-threatening events resulting from the use of antiarrhythmic therapy (AAT) in children make us cautious about its widespread application in pediatric practice [2-4]. Considering that AAT is currently the main antiarrhythmic strategy in early childhood, it is necessary to optimize treatment tactics based on evaluating the effectiveness of drugs and determining the resistance predictors [5-7].

## Material and methods

The prospective cohort study was performed between 2007 and 2017 at the Cardiology Research Institute of Tomsk. A prolonged AAT was received by 100 patients aged 0 to 7 years (2,33 years) (IQR: 0,33-5,0) with different variants of idiopathic clinically significant arrhythmias. Table 1 presents the age groups of children and types of arrhythmias.

There were following inclusion criteria: no congenital heart disease and channelopathies; no acute infectious diseases and exacerbation of chronic ones; no myocarditis signs by laboratory analysis. Indications for AAT use were: sustained paroxysmal supraventricular tachycardia (SVT) and ventricular tachycardia (VT); continuously recurring chronic SVT and VT, including in combination with supraventricular extrasystole (SVES) and ventricular extrasystole (VES), comprising 20% of the diurnal heart rate (HR) value; arrhythmogenic cardiomyopathy (ACM); heart failure signs [8-10].

The study protocol included medical history, electrocardiography (ECG), Holter monitoring (HM), echocardiography (echo). To verify the electrophysiological mechanism of tachycardia in some patients, a transesophageal electrophysiological study was performed.

When performing echo, in addition to standard measurements of intracardiac hemodynamic parameters, the deviation of the atrial volumes and left ventricle end-diastolic volume (LV EDV) from the individually predicted anthropometric standards, expressed as a percentage, was evaluated. This is necessary due to age and anthropometric heterogeneity of patients, as well as for the follow-up echo for assessment of heart changes with age. These parameters were determined automatically, according to the study protocol.

For prolonged therapy, antiarrhythmic agents of IC, II, III, and IV classes was used [11], as well as digoxin. According to recommendations of EHRA and AEPC-Arrhythmia Working Group, these agents are used both for narrow and wide QRS tachycardia, as well as for supraventricular and ventricular arrhythmias in children. Doses were consistent with the recommendations of the EHRA and AEPC-Arrhythmia Working Group [12]. However, despite the wide range of antiarrhythmic agents and their combinations, there are currently no clear recommendations for their use and criteria for the AAT effectiveness in children [13].

We propose the following gradation of the AAT effectiveness in children.

1. Effective therapy:

1.1. Elimination of paroxysmal tachycardia.

1.2. Sinus rhythm restoration in persistent and continuously recurring tachycardia.

1.3. Control of diurnal HR values in persistent and continuously recurring tachycardia until sinus rhythm restoration.

1.4. Ectopic activity decrease in premature heart beat (isolated and grouped extrasystoles, as well as

**Table 1**

**Patient's age groups and types of arrhythmia**

| | |
|---|---|
| Age (Mo; IQR; range) (years) | 2,33 (0,33-5,0); 0-7 |
| Age up to 1 year | 41/100 |
| Age 1-3 years | 23/100 |
| Age 3-7 years | 36/100 |
| Wolf-Parkinson-White Syndrome | 41/100 |
| Ectopic atrial tachycardia | 40/100 |
| Ventricular tachycardia | 18/100 |
| AV-nodal reentrant tachycardia | 1/100 |

**Note:** ectopic atrial tachycardia, including in combination with supraventricular premature beats at least 20%. Ventricular tachycardia, including in combination with ventricular ectopic beats at least 20%.

**Table 2**

**The effectiveness and duration of prolonged AAT**

| Agent | n | Duration of administration, months, Me (IQR) | Effective, n (%) | Ineffective, n (%) | Partially effective, n (%) |
|---|---|---|---|---|---|
| Monotherapy | | | | | |
| Propaphenone | 37 | 1,00 (0,33-5,00) | 5 (13,5%) | 25 (67,6%) | 7 (18,9%) |
| Propranolol | 25 | 1,00 (0,33-3,00) | 2 (8%) | 17 (68%) | 6 (24%) |
| Amiodarone | 69 | 4,00 (1,00-6,00) | 15 (21,7%) | 41 (59,4%) | 13 (18,8%) |
| Sotalol | 4 | 0,42 (0,33-3,25) | - | 2 (50%) | 2 (50%) |
| Verapamil | 5 | 0,33 (0,25-1,00) | 1 (20%) | 4 (80%) | - |
| Digoxin | 14 | 0,33 (0,33-1,00) | | 11 (78,6%) | 3 (21,4%) |
| Combination therapy | | | | | |
| Amiodarone+propranolol | 7 | 6,00 (1,83-9,00) | 2 (28,6%) | - | 5 (71,4%) |
| Sotalol+propafenone | 2 | 1,17 (0,33-2,00) | - | 1 (50%) | 1 (50%) |
| Amiodarone+Digoxin | 4 | 1,00 (0,75-6,50) | 1 (25%) | 3 (75%) | - |
| Digoxin+propranolol | 1 | 2,00 | - | - | 1 (100%) |
| Digoxin+sotalol | 1 | 2,00 | - | - | 1 (100%) |
| Digoxin+propafenone | 1 | 1,00 | - | 1 | - |

**Table 3**

**Comparative analysis of patients with effective, ineffective and partially effective therapy by age and baseline echocardiography parameters**

| Parameter | | Effective AAT (1) (n=26) | Ineffective AAT (2) (n=62) | Partially effective AAT (3) (n=12) | Intergroup p | Pair P | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | P 1-2 | P 1-3 | P 2-3 |
| Mean age, years | Me | 0,3 | 3,0 | 2,3 | <0,001 | <0,001 | 0,001 | 0,628 |
| | IQR | 0,1 -1,0 | 0,9 — 5,5 | 0,9 — 4,4 | | | | |
| LA volume,% | Me | 90,0 | 125,0 | 85,9 | 0,002 | 0,003 | 0,730 | 0,014 |
| | IQR | 76,4-116,0 | 103,7-161,5 | 79,1 — 86,5 | | | | |
| RA volume,% | Me | 91,9 | 124,0 | 105,0 | 0,001 | <0,001 | 0,283 | 0,186 |
| | IQR | 79,7-103,0 | 108,3-152,5 | 89,3-144,0 | | | | |
| LV EDV, % | Me | 98,3 | 119,0 | 111,0 | 0,080 | - | - | - |
| | IQR | 74,7-122,3 | 100,9-136,0 | 102,0-119,0 | | | | |
| LVEF,% | Me | 72,0 | 67,0 | 73,0 | 0,003 | 0,015 | 0,606 | 0,004 |
| | IQR | 65,0-79,5 | 56,5-72,0 | 69,5-76,5 | | | | |

**Abbreviations:** LA — left atrium, RA — right atrium, LV EDV — left ventricle end-diastolic volume, LVEF — left ventricular ejection fraction.

accompanied by unstable SVT or VT) to subnormal values (<1000 per day) with the elimination of grouped extrasystoles and episodes of unstable tachycardia.

2. Partially effective therapy:

2.1. The decrease in the frequency of tachycardia paroxysms ⩾50% of the baseline, extension of a period without paroxisms to 3-6 months.

2.2. The decrease in mean HR ⩾20% of the baseline.

2.3. Ectopic activity decrease in premature heart beat ⩾50% of the baseline.

**Table 4**

**The AAT efficiency predictors based on univariate logistic regression analysis**

| Parameter | P | OR | 95% CI | | Match rate (%) |
|---|---|---|---|---|---|
| | | | Lower limit | Upper limit | |
| Age | 0,001 | 0,513 | 0,349 | 0,754 | 75,0 |
| ACM | 0,003 | 4,608 | 1,703 | 12,467 | 72,7 |
| LA volume | 0,012 | 0,971 | 0,949 | 0,994 | 80,9 |
| RA volume | 0,001 | 0,661 | 0,524 | 0,835 | 85,7 |
| LA | <0,001 | 0,763 | 0,661 | 0,882 | 74,4 |
| LA1 | 0,001 | 0,781 | 0,676 | 0,903 | 85,3 |
| LA2 | 0,001 | 0,731 | 0,606 | 0,881 | 82,4 |
| RA1 | <0,001 | 0,751 | 0,652 | 0,866 | 82,5 |
| RA2 | <0,001 | 0,734 | 0,628 | 0,859 | 81,3 |

**Abbreviations:** ACM — signs of arrhythmogenic cardiomyopathy, LA volume — volume of the left atrium (ml), RA volume — volume of the right atrium (ml), LA — anterior posterior dimension of the left atrium (mm), LA1 — lateral-medial dimension of the left atrium (mm), LA2 — superior-inferior dimension of the left atrium (mm), RA1 — lateral-medial dimension of the right atrium (mm), RA2 — superior-inferior dimension of the right atrium (mm), OS — odds ratio, CI — confidence interval.

2.4. Partially effective therapy also included cases when in the first days and weeks the criteria for effective therapy were achieved and then efficiency was decreased, which in most cases required AAT modification. Therapy was considered ineffective if it did not meet any of the above criteria.

3. At the beginning, we were guided by the trial and error method. Firstly, agent with the shortest half-life and lowest risk of side effects was prescribed. If one agent was ineffective, another was prescribed after five half-lives of the previous one.

Over the entire follow-up, 50 (50%) children received 1 agent, 33 (33%) — 2 agents, 8 (8%) — 3 and 4 agents, and 1 (1%) — 6 agents in sequence. With resistance to antiarrhythmic monotherapy in 19 patients, combination therapy was prescribed — in 16 children 1 combination was used, in 3 children — 2 combinations in sequence.

Children receiving amiodarone were evaluated every 3 months for liver and thyroid function.

We assessed HM and echo parameters initially, at 5-8 days after the effective therapy criteria were reached, and 6 months after the AAT discontinuation.

The mean follow-up period for patients with effective therapy was 5,3±2,1 years (2 to 8 years).

**Statistical analysis.** Statistical processing of the results was carried out using R 3.0.2 software. Description of quantitative characters is presented as median and interquartile range — Me (Q1; Q3). Comparison of two independent samples was performed using the Mann-Whitney test, three or more — Kruskal-Wallis test. When conducting multiple pairwise comparisons of the samples, the significance level achieved in the study was adjusted with Bonferroni correction. The quantitative changes were evaluated using the Wilcoxon test.

The assessment of unfavorable prognosis probability and the identification of significant predictors of an adverse outcome were performed using multivariate logistic regression analysis. The creation of a forecast model for the AAT effectiveness was carried out using discriminant analysis. The statistical significance of the model was evaluated by the Wilks's

**Table 5**

**CLDF values in centroids of effective and ineffective AAT groups**

| Parameter | Function |
|---|---|
| Effective therapy | -1,276 |
| Ineffective therapy | 0,300 |

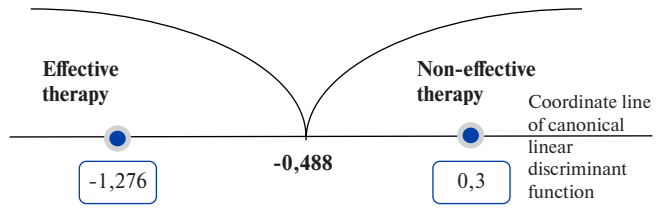


**Fig. 1.** Graphical representation of the discriminant function.

lambda distribution. Goodness of fit of the real observation distribution and the forecast, the Percentage Correct method was used, and the sensitivity and specificity of the model were evaluated. The quality of the model was also evaluated using ROC analysis with the determination of the area under the ROC curve (AUC). Statistical significance was considered as $p<0,05$.

The study was conducted in accordance with Good Clinical Practice guidelines and the principles of Declaration of Helsinki; the study protocol was approved by local independent ethics committees. All legal representatives of patients completed the informed consent.

## Results

The effectiveness and duration of antiarrhythmic therapy are presented in Table 2. The criteria for effective therapy were obtained using amiodarone, propafenone, propranolol and verapamil, as well as AAT combinations: amiodarone+propranolol, amiodarone+digoxin.

A proarrhythmic effect was obtained in 1 patient, who, against the background of amiodarone taking, underwent parenteral esmolol administration to suppress tachycardia paroxysm. As a result of this combination, the patient had the symptomatic bradycardia, which required resuscitation. There were no cases of proarrhythmia in other patients.

The main reasons for discontinuation were inefficiency and delayed resistance of agents after the initial effect.

Absolute effectiveness criteria were achieved in 26 (26%) of 100 patients receiving prolonged AAT, partial effectiveness — in 12 (12%) patients. Therapy was ineffective in 62 (62%) patients.

When comparing the AAT effectiveness in patients with various electrophysiological types of arrhythmias, there were no statistically significant differences between the variants of tachycardia and the clinical manifestations of heart failure (class I-IV according to NYHA classification).

During effective therapy, reducing clinical symptoms of heart failure was noted in 11 patients was observed.

A comparative analysis of patients with effective, ineffective, and partially effective therapy by age and intracardiac hemodynamic parameters is presented in Table 3. Among patients with effective AAT, there were more children under the age of 1 year ($F=20,713$; $p<0,001$) without ACM ($\chi^2=11,618$; $p=0,003$). Echo results showed that in the effective therapy group, the median values of initial atrial volume were in normal range. In patients with an initial atrial volume increase, AAT was ineffective. LV ejection fraction (EF) in patients with effective AAT was statistically significantly higher compared to patients with ineffective AAT.

Univariate logistic regression analysis showed that the age, atrial dimension and volume, as well as a qualitative character of ACM signs, are independent predictors of the AAT effectiveness (Table 4).

The results of the analysis indicate that with an increase in age by 1 year, the probability of effective therapy decrease by 48,7%. The presence of ACM signs reduces the chance of effective results by 4,6 times. With an increase in the volume of the right (RA) and left atria (LA) by 1 ml, the probability of high AAT effectiveness decrease by 33,9% and 2,9%, respectively. With an increase in atrial dimensions by 1 mm, the chances of an effective results are reduced by 21,9-26,9%.

Discriminant analysis allowed us to develop a multidimensional model for predicting the effectiveness of continuous therapy (Patent № 2611954 of 03.17.2017). As a criterion for dividing into groups, a sign of the AAT effectiveness was used.

During the analysis, predictors of the AAT effectiveness were determined — patient's age, RA and LA volumes as a percentage, LVEF, mean and maximum HR according to the HM.

Equation for calculating canonical linear discriminant function (CLDF) is built:

CLDF = -3,359 + 0,017 * RA volume (%) + 0,001 * LA volume (%) — 0,001 * LVEF — 0,013 * mean HR + 0,009 * max HR according to HM + 0,296 * age, years.

CLDF values in group centroids are presented in Table 5:

The decision rule for the classification of objects is formulated as follows: the object will be assigned to the class closer to the centroid of which is the calculated CLDF value (Fig. 1).

The model is statistically significant (Wilks's lambda distribution 0,716, p=0004). The total percentage of correctly classified cases is 81%, sensitivity — 78,4%, specificity — 91,7%.

The high quality classification using the proposed model is also confirmed by the ROC analysis: the area under the ROC curve was 0,895 (95% CI 0,814-0,977, $p<0,001$).

The proposed method for predicting the AAT effectiveness is demonstrated in the following clinical observations.

**Clinical example 1.** Patient M., age of 22 days. There are complaints from parents about tachycardia

episodes accompanied by lassitude, refusal to feed. It is known that the first episode of tachycardia occurred during delivery. After this, tachycardia paroxysms up to 4 hours; it stopped after intravenous bolus infusion of an adenosine solution (0,1 mg/kg), as well as a bolus infusion of amiodarone (5 mg/kg for 30 min). Follow-up control showed a tendency toward an increase in tachycardia episodes, which began to occur daily and became continuously recurring. Based on the history data, physical examination, survey including ECG monitoring during and outside tachycardia episodes, HM, transesophageal electrophysiological study (TEEPS), and echo, the following diagnosis was established: Latent WPW syndrome. Paroxysmal orthodromic tachycardia. Class II heart failure (according to NYHA classification).

The markers for constructing an AAT effectiveness model are as follows:

Age: 0,08 years (1 month)
RA volume, %: 72,5%
LA volume, %: 71,8%
EF, %: 87%
Mean HR according to HM: 137 bpm
Maximum HR according to HM: 199 bpm
Forecast for the AAT effectiveness:

CLDF = -3,359 + 0,017 * 72,5 + 0,001 * 71,8 — 0,001 * 87 — 0,013 * 137 + 0,009 * 199 + 0,296 * 0,08.

CLDF = -2,11

This value indicates a high probability of the effective AAT.

As a result of the AAT selection, the patient was prescribed amiodarone powder at a loading dose of 10 mg/kg/day for 15 days, followed by 5 mg/kg/day. During the administration of loading dose, frequency of tachycardia episodes decreased and starting from the 16th day of therapy, it did not relapsed. In order to prevent tachycardia, the patient was prescribed prolonged therapy with amiodarone at a dose of 5 mg/kg/day. Given the normal state of health and the absence of tachycardia paroxysms, amiodarone was discontinued after 4 months of therapy. There were no tachycardia episodes over the next 5 years of follow-up.

**Clinical example 2.** Patient I., 11 months of age, was admitted to the Division of Pediatric Cardiology with complaints from his parents about tachycardia, sweating, lassitude, fatigue, loss of appetite. After the examination, including ECG, HM, echo, the following diagnosis was established: Continuously recurring atrial tachycardia. Class III heart failure.

The markers for constructing an AAT effectiveness model are as follows:

Age: 0,92 years (11 months)
RA volume, %: 159 %
LA volume, %: 199%
EF, %: 32%
Mean HR according to HM: 194 bpm
Maximum HR according to HM: 277 bpm
Forecast for the AAT effectiveness:

CLDF = -3,359 + 0,017 * 159 + 0,001 * 199 — 0,001 * 32 — 0,013 * 194 + 0,009 * 277 + 0,296 * 0,92.

CLDF = -0,25

This value indicates a high probability of the ineffective AAT.

Given that the first-line treatment of arrhythmia in early childhood is AAT, in the department, there was agent selection including digoxin, propafenone, propranolol, amiodarone. Therapy was ineffective. Against the background of continuously recurring tachycardia with a high mean HR according to HM, ACM according to echo, and circulatory failure increase, the patient underwent RFA of the right atrial ectopic foci.

## Discussion

The clinical and prognostic value of arrhythmias is determined by the hemodynamic manifestations of arrhythmia — the ACM development [14-16]. Children of the first years of life constitute a risk group for the ACM development due to high HR during tachycardia, its tendency to chronization, and drug resistance [17-19]. Atrial tachycardia is the most common cause of ACM in children. In addition, the ACM is susceptible to both children with SVT due to accessory atrioventricular connections and ventricular arrhythmias, which are characterized by a tendency to chronization, and drug resistance [8, 9, 17, 20].

As regards the management strategy, there is no universal approach. A number of researchers report high efficacy of medication in infants and toddlers and recommend treatment regimens that include combinations of two or even three antiarrhythmic agents [21-25]. However, a large number of publications indicate the limited effectiveness and safety of AAT for the management of arrhythmias in children [2-6, 25]. Despite the fact that various combinations of AAT can increase its effectiveness, it increases the risk of side effects, including mortality, in particular, with a combination of classes I and III agents [18].

In a multicenter retrospective study by Seslar SP, et al. it has been shown that AAT during hospitalization is effective and safe in children under the age of 1 year with idiopathic SVT. It should be noted that the average hospital stay for patients was 4 days. It depended on the number of drugs taken and the need

for patients to stay in the intensive care unit. However, this study has significant limitations — there were only assessment of therapy beginning and no prospective follow-up [21]. The authors of another retrospective cohort study, evaluating the effectiveness of AAT in children hospitalized in the intensive care unit, indicate the lack of data on further outpatient monitoring, changes in treatment regimens, side effects of therapy, recurrence of arrhythmia after drug withdrawal [13]. Whereas precisely these data specify the expediency and prospects of the therapy, the initial effectiveness of AAT with its subsequent loss and arrhythmia recurrence is well known. Most publications on AAT in children have limitations associated with small sample sizes, the retrospective design of the study, and the lack of data on long-term outcomes [26, 27]. According to Maid G, et al., basic principles of AAT in pediatric practice, dosages and intervals for AAT administration are taken from "adult" arrhythmology without taking into account the physiological features of children. Therefore, many authors point to the need for multicenter, randomized, placebo-controlled clinical trials. [6].

The results of our study show that children under the age of 1 year without ACM signs are more likely to have an effective AAT results. Factors that increase the risk of ineffective AAT include older children, severe ACM manifestations according to echo. Similar results are presented in the study by Ge H, et al., where the predictors of the AAT effectiveness are early age and the paroxysmal tachycardia, which usually does not lead to the ACM formation [28]. Our data are consistent with the paper by Sanatani S, et al., where 44 patients under the age of 6 months were studied. Authors revealed that reduced LVEF was a predictor of refractory tachycardia, while the nosologic unit of arrhythmia did not significantly affect the result of therapy [29]. It is noteworthy that, according to the results of the above study, early manifestation of arrhythmia was not the key to successful therapy. On the contrary, the present study showed that the early age of the patient is an independent predictor of the effective AAT. Similar data were obtained by Salerno JC, et al. Authors reported a high probability of spontaneous resolution of atrial ectopic tachycardia after successful drug therapy if it occurs in the first year of life, but this trend rarely remain at an older age [22].

Based on the data obtained, a multivariate model for predicting the effectiveness of a prolonged AAT has been developed to determine individual management of children with arrhythmias. This model will allow avoiding prolonged therapy and timely using other treatment methods in case of predicting an ineffective AAT.

## Conclusion

Factors affecting the AAT efficiency are age and state of intracardiac hemodynamic parameters. Prolonged AAT is indicated for young children with tachyarrhythmias not accompanied by structural changes in the heart. It should be noted that this category of children has a high chance of spontaneous resolution of arrhythmias, and after the discontinuation of effective therapy, arrhythmia may not relapse during further follow-up. In patients of any age, and especially after 1 year of life with echocardiographic signs of ACM, an ineffective AAT should be assumed and RFA should be planned.

**Conflicts of Interest:** nothing to declare.

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# Atrial fibrillation and gastroesophageal reflux disease: association mechanisms, treatment approaches

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The article is devoted to assessing the relationship of atrial fibrillation (AF) and gastroesophageal reflux disease (GERD). We studied possible anatomical correlations, common risk factors and mechanisms of AF development in patients with gastroesophageal reflux. We demonstrated the problems of the treatment of such patients, since a number of studies have proved the possibility of using proton pump inhibitors in the treatment of AF. In other cases the arrhythmogenic effect of these drugs was obtained. Treatment of AF by catheter ablation most commonly worsens the course of GORD and can lead to the development of fatal complications. Large-scale prospective researches are needed for further detailed study of AF and GERD associations, as well as tactics for management of these patients.

**Key words:** gastroesophageal reflux disease, proton pump inhibitors, radiofrequency ablation, atrial fibrillation.

**Conflicts of Interest:** nothing to declare.
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Atrial fibrillation (AF) is a common rhythm disorder with a 3% approximate frequency in adults aged 20 years and older [1, 2]. By 2030, in the countries of the European Union, AF prevalence can reach 14-17 million patients [3]. AF is independently associated with a twofold increase in the risk of all-cause mortality in women and 1,5-fold — in men [4].

Concomitant cardiovascular disease and many other comorbidities are often predisposing factors for AF. It increases the risk of recurrent arrhythmias and the incidence of complications. Identification of such factors, its prevention and timely modification are necessary for choosing the optimal strategy of successful AF control and complications' preventing [5].

In the last decade, interest in functional relationship between the gastrointestinal (GI) tract, in particular the esophagus, and the cardiovascular system has renewed. In the past, supposed association between upper GI and cardiovascular diseases was defined as Roemheld syndrome, where irritant esophagogastric stimulus cause not only chest pain, but also arrhythmias and increased blood pressure. Currently, researchers pay more and more attention to the mechanisms of arrhythmias associated with pathological gastroesophageal reflux, as well as its pharmacotherapy [6].

Several studies have reported a correlation between gastroesophageal reflux disease (GERD) and AF. The coincidence of acid reflux and AF paroxysm was shown with simultaneous pH meter using and 24-hour Holter monitoring [7]. It was found that in a number of arrhythmias, vegetative imbalance was caused by gastroesophageal reflux [8]. After modification of other risk factors, a strong correlation between GERD and AF was demonstrated [9, 10]. At the same time, in a retrospective study involving 5288 residents of Olmstead County, Minnesota, there was no correlation between GERD and AF [11].

Thus, the relationship between AF and GERD cannot be considered as completely studied due to the limited number of studies and sample sizes, but it is of scientific and practical interest.

**Potential common mechanisms between GERD and AF**

**Anatomical interactions.** Inflammatory and infiltrative changes in the left atrium (LA) can be associated with the pathogenesis of GERD or AF, especially when the LA contact with the lower esophagus. Atrial inflammatory response associated with chronic AF, theoretically determines the GERD mechanisms by anatomical connection between the esophagus and the LA. The LA posterior wall and the esophagus are separated by a layer of tissue about 5 mm thick. Anatomical interactions between the esophagus and the LA are not well understood. Computed tomography data before and during the contrast esophagiogram showed that esophageal location may differ. In some patients, the esophagus is closer to the left pulmonary vein, while in others to the right pulmonary vein. The periesophageal plexus, which regulates the gastric motility, can branch above or below the LA [12].

When studying the AF prevalence in patients with hiatal hernia from 1976 to 2006 at the Mayo Clinic in Rochester, the authors concluded that the AF development often, especially in young patients, is associated with chronic mechanical LA compression that underlies future AF [13]. In patients with a hiatal hernia, arrhythmias may be a result of mechanical compression of the LA anterior wall by food passing through the esophagus. If this happens regularly and lasts for a long time, over many years, it can lead to chronic ischemia of this zone and development of reentry arrhythmia [14].

**Autonomic activation.** The occurrence of arrhythmias in patients with GERD is associated with an imbalance of cardiac autonomic effects. The process can be started by the action of a refluctant on the reflexogenic zones of the distal esophagus and the development of viscero-visceral reflexes mediated by the vagus.

Chemical, electrical and mechanical stimulation of the esophagus alters the sympathovagal balance. Several observations confirm the important role of the autonomic nervous system in AF initiating and maintaining. The effect of vagal stimulation on atrial refractoriness is heterogeneous, since the distribution of parasympathetic nerve endings and/or muscarinic receptors is different. The increased vagus activation in GERD patients creates an arrhythmogenic substrate for the reentry mechanism, and thereby increases the AF risk.

Stimulation with hydrochloric acid is associated with an increase in vagus activity [15]. Gastroesophageal reflux causes a local inflammatory process that can directly change the autonomic innervation of the esophageal mucosa and stimulate contiguous vagus. Such excessive vagus stimulation creates the basis for the AF development [16, 17].

Although both sympathetic and parasympathetic components may play a role in the AF development, the cholinergic component is probably the most important. Electrical stimulation of LA ganglion plexuses (located on the LA posterior wall, close to the esophagus) or autonomic nerve endings cause spontaneous stimulation of the pulmonary veins and subsequent AF development [18]. Gastroesophageal reflux may be a trigger for AF in paroxysmal AF.

**Table 1**

**Studies on the PPIs use in patients with GERD and AF**

| Year of publication | Authors | Study design | Main results |
|---|---|---|---|
| Studies where the positive PPIs effect has been proven | | | |
| 2006 | Cuomo R, De Giorgi F, Adinolfi L, et al. | Observational prospective control study. 32 patients with GERD and arrhythmia and 9 patients with GERD only. Valid questionnaires and endoscopy were used to establish GERD. Holter ECG monitoring, esophageal manometry, acid perfusion test and 24-hour pH monitoring were performed. Within 3 months the PPIs maximum dose was prescribed. | PPI therapy was effective in 56% of patients; significant cardiac symptom improvement was recorded. |
| 2006 | Gerson LB, Friday K, Triadafilopoulos G. | Observational prospective study. Three patients had an association of heartburn, acid regurgitation and tachycardia. Patients underwent both an ambulatory 24-hour esophageal pH monitoring and Holter monitoring. Antireflux therapy lased at least 7 days. | Symptoms of GERD and AF decreased with omeprazole therapy. |
| 2015 | Chen KP, Lee J, Mark RG, et al. | Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC-II) of 8457 patients taking PPIs or H2 receptor blockers. | The use of PPIs and H2 receptor blockers was not associated with an increased risk of arrhythmia (OR 0,85; 95% CI 0,72-1,01, p=0,07; OR 0,88; 95% CI 0,66-1,18, p=0,40, respectively). |
| Studies where the positive PPIs effect has not been proven | | | |
| 2010 | Marcus GM, Smith MM, Scheinman MM, et al. | "Case-control" study, the use of PPIs in 80 patients with focal tachycardia, the control group consisted of patients with recurrent rhythm disturbances due to anatomical abnormalities. 12-lead ECG in and electrophysiological test was conducted. | The proportion of patients with focal atrial tachycardia and PPIs use was significantly higher than in the control group (p=0,009). After adjustment, the use of PPIs was associated with a greater risk of focal arrhythmia (OR 3,6; 95% CI 1,2-11,1, p=0,025) and focal atrial arrhythmia (OR 4,5; 95% CI 1,3-15,7, p=0,018). |
| 2012 | Huang CC, Chan WL, Luo JC, et al. | Prospective study. 29688 patients with GERD from the Taiwan National Health Insurance Database. Control group included 29597 people without GERD or history of arrhythmias. GERD was diagnosed with ICD-9 codes; AF — with ICD-9, ECG and Holter monitoring. Participants took PPIs; follow-up lasted three years. | Those receiving PPI therapy had an increased risk of AF (RR=1,46; 95% CI 1,15-1,86, p=0,002). Patients with GERD who did not receive PPIs did not have an increased risk of AF. |
| 2015 | Odashiro K, Yasuda S, Yokoyama T, et al. | Single-center study. Patients with AF and GERD (n=27). Questionnaires on the symptoms of GERD and AF before and after PPI therapy for 3 months was used. From this group, 5 patients with pacemakers were selected with ongoing PPI therapy for 6 months. | Common symptoms of GERD (p<0,001), reflux (p<0,001) and regurgitation (p=0,013) were significantly improved with PPI. The frequency and duration (p=0,001), severity (p<0,001) of AF symptoms were decreased. Analysis of the device data did not confirm significant changes regarding the number (p=0,138) and the maximum duration (p=0,345) of AF paroxysms. |

Muscarinic acetylcholine receptors are the primary neurotransmitters of parasympathetic cardiac control. Stimulation of the muscarinic receptor with acetylcholine activates G-protein-linked potassium currents, leading to a reduction in the duration and effectiveness of the atrial refractory period [16].

It is less known that AF can also cause GERD, since an enlarged LA can compress or irritate the contiguous lower esophagus [19].

**Inflammation.** Another assumption is that as a result of reflux esophagitis, an inflammatory process develops in the esophageal wall and then can

**Table 2**

**Outcomes and complications of RFA use in AF patients**

| Year of publication | Authors | Study design | Main results |
|---|---|---|---|
| 2013 | Reddy YM, Singh D, Nagarajan D, et al. | A prospective case-control study. 30 patients with AF, GERD and/or IBS (group 1), 30 patients with AF without GERD or IBS (group 2). | During RFA, more patients in group 1 had a "vagal response" (60 vs.13%; p<0.001). After 1 year, 93% of patients showed no signs of AF without differences between the two groups. |
| 2014 | Knopp H, Halm U, Lamberts R. | Cohort study. 425 patients with symptomatic AF who underwent RFA of the LA. EGD was performed by everyone 1-3 days after the procedure. Patients did not have GI tract symptoms. | Pathological symptoms were observed in 77% of patients and included gastric erosion (22%), esophageal erythema (21%), gastroparesis (17%), esophageal hernia (16%), reflux esophagitis (12%), thermal esophageal lesion (11% ) and suspected Barrett's esophagus (5%). |
| 2015 | Tolone S, Savarino E, Docimo L. | Clinical case. 65-year-old man with drug-resistant paroxysmal AF. Before the RFA, patient underwent high resolution manometry and pH-impedance monitoring. Pathology is not revealed. | After 8 weeks, manometry showed spastic hypercontraction, while pH-impedance monitoring did not show GERD signs. |
| 2015 | Chavez P, Messerli FH, Dominguez AC, et al. | A systematic review of observational cases of AEF after ablation procedures in accordance with the PRISMA protocol, 53 cases. | The average interval between the procedure and the complication was 20±12 days. AEF was observed in 12 patients who underwent surgical RFA, and in 41 patients with percutaneous RFA. Fever (n=44), neurological disorders (n=27) and hematoma (n=19). Computed tomography of the chest (n=27) was the preferred diagnostic test. Patients who did not perform the operation were more likely to die (34% vs. 83%; p<0,05). |
| 2017 | Han HC, Ha FJ, Sanders P, et al. | Review of PubMed and Embase sources. Of 628 references, 120 AF cases with catheter ablation were identified. | The clinical performance of AEF manifested on day 21: fever (73%), neurological (72%), GI (41%) and cardiac (40%) symptoms. |
| 2017 | Orosey M, Garg L, Agrawal S, et al. | Two clinical cases. 1) A 46-year-old man with persistent AF and multiple cardioversion underwent catheter ablation.<br>2) A 63-year-old woman with paroxysmal AF underwent ablation with pulmonary vein isolation. | 1) Post-ablation EGD revealed an esophageal ulcer (1,3 cm). 21 days later, neurological symptoms manifested, EGD confirmed the presence of AEF.<br>2) After 1 month, EGD revealed an esophageal ulcer; during an emergency surgery — LA defect. |

**Abbreviations:** AEF — atrioesophageal fistula, GI — gastrointestinal, IBS — irritable bowel syndrome, EGD — esophagogastroduodenoscopy.

involve closely located LA wall with subsequent AF development. Observational studies also suggest that it is not the symptoms of GERD in general, but specifically the endoscopic signs of esophagitis that are associated with an increased AF risk [15]. The spread of the local inflammatory process through the esophageal wall can also cause local pericarditis or atrial myocarditis due to the esophagus and LA closeness.

In patients with AF without structural heart disease, myocarditis can be detected in 66% of patients. Cytokines have been shown to play an important role in the AF pathophysiology [16, 20]. Esophageal mucosa inflammation affects local receptors, which can cause afferent and efferent reflexes. Inflammatory factors, including oxidative stress, leukocytes and cytokines, such as interleukin (IL) -6, IL-8, are known to cause GERD [21].

**Thus, AF and GERD can be considered as complementary partners with common inflammatory mediators that support and lead to the progression of these diseases.**

**Common risk factors**

Many clinical and epidemiological studies have found that a significant percentage of patients with AF have coexisting diseases, such as metabolic syndrome, non-alcoholic fatty liver disease, obesity, sleep apnea [5].

The development of GERD correlates with these same common diseases: obesity [22], metabolic syndrome [23], sleep apnea [24]; obesity increases the gastroesophageal pressure gradients [25].

These lifestyle-related diseases are accelerated by proinflammatory, procoagulant and profibrotic mediators, which also alter atrial electrophysiology and microstructure, which contribute to structural remodeling in AF.

**Management of patients with GERD and AF**

The management of patients with GERD and AF is an important problem that has not been completely resolved [15]. It has been proven that modification of cardiovascular risk factors, especially obesity, prevents the recurrence and progression of AF and improves the ablation outcome [26, 27]. Along with this, lifestyle changes and weight loss should be considered prerequisites for effective antireflux therapy [28].

**The effect of antisecretory therapy on AF.** A number of authors consider that acid-suppressive therapy used to treat GERD has positive effects on AF [29]. Proton pump inhibitors (PPIs) can be an addition to standard antiarrhythmic treatment by improving AF symptoms [7, 8, 30] (Table 1) and facilitating the restoration of sinus rhythm, with the advantage that it are less expensive and have fewer side effects [31].

These studies show that the therapeutic effects of PPIs in AF are mediated by the elimination of the trigger for the cardiogastric reflex caused by acid reflux. In addition to acid suppression by blocking the proton pump (hydrogen potassium ATPase) in the gastric mucosa, PPIs have an antioxidant and anti-inflammatory effect [32] — it blocks the production of nitric oxide *in vitro* and decreases the secretion of pro-inflammatory cytokines [33]. Scanning electron microscopy revealed leukocyte infiltration in the LA endothelium in patients with valvular AF after valve replacement open heart surgery [34]. PPIs are able to suppress the activity of leukocytes, epithelial and endothelial cells, which are indirectly activated by changes in intracellular pH and homeostasis [29]. The role of hydrogen potassium ATPase in the heart function regulation was confirmed in laboratory conditions: gastric isoforms of hydrogen potassium ATPase and receptors for PPIs binding are present in mammalian heart cells. Scientists have concluded that PPIs can have antiarrhythmic and cardioprotective effects [35].

However, not all studies clearly demonstrated the positive effect of PPIs in patients with GERD and AF [36, 37] (Table 1), since there are data regarding the potential proarrhythmic effect of PPIs [38]. A possible mechanism is associated with the fact that it can cause hypomagnesemia and concomitant electrolyte disturbances, including hypocalcemia and hyperpotassemia, provoking life-threatening arrhythmias [39, 40].

The pathogenesis of hypomagnesemia is still not completely clear; several studies have suggested PPI-induced impaired magnesium absorption in the GI tract. Although most oral magnesium is absorbed passively through the paracellular pathways between enterocytes, PPIs affect the functioning of the second transport system of magnesium — transcellular cation channels. It allows adaptation to low magnesium intake by increasing of its fractional absorption. Chronic use of PPIs is believed to impair this adaptive intestinal response to low dietary magnesium intake [41-44]. Hypocalcemia, secondary to hypomagnesemia, develops due to functional hypoparathyroidism [45], as well as due to a decrease of calcium bioavailability as a result of achlorhydria [46].

**The effect of AF therapy on GERD.** Non-pharmacological AF treatment includes radiofrequency ablation (RFA). Three main mechanisms of the RFA negative effect on the GERD are distinguished: 1) periesophageal vagal injury 2) direct thermal damage to esophageal mucosa and 3) atrioesophageal fistula formation [18, 47] (Table 2). The RFA itself can lead to an increase in the number of new GERD cases by 19%, since the appearance of reflux is associated with direct vagal stimulation and a decrease of esophageal sphincter tone, as well as with a long lying position of patients during the procedure. Moreover, the "vagal response" can be caused both by a direct stimulus to the vagus nerve, which is adjacent to the heart, and by thermal damage to the esophageal vagal fibers. It causes an imbalance in favor of excitatory innervation with characteristic changes in the esophageal motility [48].

Another esophageal lesion caused by the ablation is thermal trauma. It varies in severity from erythema, esophagitis and ulceration to necrosis and depends on the RFA technique, as well as on the maximum energy arrived at the posterior wall. Some authors consider that esophageal ulceration may be a potential precursor to a life-threatening condition — atrioesophageal fistula [49, 50] with a complication rate of 0,03-1,5% per year [51, 52]. Death is usually inevitable, although survival is possible with timely diagnosis and emergency surgery.

The clinical manifestation of GERD is chest pain, in connection with which general practitioners may mistakenly prescribe cardiac drugs to these patients. Although calcium channel blockers and nitrates can be effective for chest pain by eliminating the spastic motility of the esophagus [53], these drugs cause relaxation of the lower esophageal sphincter and increase acid reflux [54].

A number of authors have shown that anticoagulants' taking, in particular warfarin, is an independent risk factor for symptomatic GERD [54]. The RELY study demonstrated that, against the background of dabigatran administration, an increase in the incidence of gastroenterological symptoms such as dyspepsia, gastroesophageal reflux, impaired motility of the upper GI tract, and damage to the gastroduodenal mucosa was noted [55]. These pathologies occurred in 16,9% of patients, and 4% had to stop dabigatran therapy. Similar results were obtained by Japanese doctors: dabigatran-induced esophagitis was detected in 20% of endoscopic studies [56].

Mechanisms of gastroenterological side effects of dabigatran are not fully understood. It was assumed that this is due to the release of tartaric acid from the capsule and irritation of the mucosa. It is believed that if dabigatran is taken in accordance with the recommendations (in an upright position, with food and washed down with water), then adverse effects can be significantly minimized. Also, PPIs should be added to therapy, although their effect on the improvement of side effects has not been proven [57].

## Conclusion

Clinicians should be aware of a possible cardiogastric interaction between GERD and AF. There is a need for further studies to determine whether there are true causal relationships (independent of concomitant diseases), whether the identification and treatment of GERD, especially esophagitis, can help to restore and maintain sinus rhythm. It is important to determine whether the pharmacological or non-pharmacological potential of GERD treatment plays a role in the long-term management of AF patients. Large-scale prospective studies are required to determine the indications for the PPIs use for a specific group of patients with AF.

**Conflicts of Interest:** nothing to declare.

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# Assessment of heart transplant recipients survival based on ultrasound diagnostic methods and immunological screening of antibodies to leukocyte donor antigens

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**Aim.** To create a mathematical model for predicting an assessment of the risk of antibody-mediated rejection (AMR) and analyze the survival of recipients with antibodies to leukocyte donor antigens.

**Material and methods.** A single-center study was conducted on the basis of S.V. Ochapovsky Regional Clinical Hospital № 1. During the 7 years 181 heart transplant recipients were observed. Based on the AMR crisis and detected antibodies to leukocyte donor antigens (HLA), 5 groups were identified: group 1 (n=10) — donor-specific antibodies (DSA) and AMR crisis, group 2 (n=7) — patients without DSA and AMR crisis, group 3 (n=17) — patients with antibodies to HLA, without AMR crisis, group 4 (n=11) — with AMR crisis, without identified antibodies to HLA, group 5 (n=87) — patients, not having antibodies to HLA and signs of both AMR and cell-mediated rejection (according to endomyocardial biopsy). The recipients underwent immunological tests, 2D-speckletracking echocardiography (2D-STE) and transthoracic echocardiography (TTEchoCG). Statistical methods were used to assess the results.

**Results.** Predictors of the severe form of AMR in TTEchoCG are: left ventricle enddiastolic diameter, interventricular septum thickness, ejection fraction, right ventricle volume. Predictors were determined using the 2D-STE method: global longitudinal peak strain, sensitivity (SE) — 86,2%, specificity (SP) — 90,4%; radial strain, SE — 75,8%, SP — 84,5%; circular strain, SE — 78,6%, SP — 84,4%. When taking into account the indicators of the global longitudinal peak strain of the left ventricle and the longitudinal peak strain of the right ventricle, SE increases to 91,9%, SP — 94,6%, with p<0,001. The survival rate of patients with identified post-transplant (*de novo*) donor-specific antibodies of the late period is 40%, without identified donor-specific antibodies — 68%. Dedicated predictors are used for mathematical prediction of AMR risk.

**Conclusion.** The relationship between immunological changes and data of TTEchoCG, deformation parameters and mechanics of a heart transplant was revealed. The presence of *de novo* DSA decline the survival, increases the risk of AMR, and contributes to the development of coronary artery disease. The proposed AMR risk prediction model will improve the long-term results of heart transplantation.

**Key words:** humoral rejection, antibodies to donor antigens, donor-specific antibodies, global longitudinal peak strain, 2D-speckle-tracking echocardiography, artificial neural network, survival.

**Conflicts of Interest:** nothing to declare.

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To date, the crisis antibody-mediated rejection (AMR) remains an important diagnostic and therapeutic problem in heart transplantation [1]. Clinical practice discusses the importance of early and late rejection, the effect of human leucocyte antigens (antibodies to HLA, HLA AB), donor-specific antibodies (DSA) and non-DSA identified in the post-transplant period (*de novo*) on the development of complications and long-term outcomes of heart transplantation (HT) [2, 3]. Researchers from different countries have concluded that *de novo* HLA AB have an adverse effect on the prognosis of heart recipients. At the same time, the presence of *de novo* HLA AB, without signs of transplant dysfunction, does not always associated with AMR crisis [4].

The use of easily available, non-invasive conventional transthoracic echocardiography (TTE), which is the first stage of the crisis diagnostics, allows us to identify changes in parameters that correlate with a detailed picture of heart transplant rejection. However, TTE and Doppler ultrasonography are not early predictors of rejection due to high variability in cardiac recipients. [5]. The use of more complex, applied 2D-speckle-tracking echocardiography (2D-STE) technique, which approved oneself since the beginning of the 20th century, helps to further quantify the function of longitudinal, circular and radial fibers of the left ventricle, longitudinal fibers of the right ventricle, as well as heart mechanics [6 ]. Many sources of literature indicate the relationship of morphological changes in the early stage of rejection and diagnostic parameters of the 2D-STE technique, which allows it to be used for a more in-depth study of cardiac transplant dysfunction [6].

In our study, artificial neural network was used to assess AMR risk. It allowed us to increase the accuracy of the results.

The aim of this study was to develop an artificial neural network to assess the AMR risk, based on important risk factors identified through routine studies in clinical practice, followed by predicting the survival of cardiac transplant recipients.

## Material and methods

In the "S. V. Ochapovsky Research Institute of Regional Clinical Hospital № 1" in Krasnodar, the analysis of heart recipients' (n=181) monitoring from 2010 to 2017 was conducted. There were more men — 82,87% (n=150), women accounted for 17,13% (n=31), and the average age of the recipients was 48±11 years. Patient survival over 7 years of follow-up was 72%. All heart recipients were examined according to the currently accepted algorithm in the medical center. Depending on the histological data of the AMR crisis and the detected *de novo* HLA AB, the studied recipients were divided into 5 groups: group 1 (n=10) — patients with DSA and AMR crisis, group 2 (n=7) — patients with non-DSA and AMR crisis, group 3 (n=17) — patients with HLA AB, without AMR crisis, group 4 (n=11) — patients with AMR crisis, without identified HLA AB at the time of the study, and group 5, control (n=87) — patients without HLA AB and signs of both AMR and cell rejection according to endomyocardial biopsy (EMB).

**Immunology research.** The screening and identification of HLA AB in the posttransplant period, *de novo*, was carried out in accordance with the schedule adopted at the medcial center: at 1-3-6 and 12 months, and also according to emergency indications in cases of suspected AMR crisis. Screening and identification was made by Luminex Multiplex Assays using LIFECODES reagents.

**Conventional TTE**. The conventional TTE was performed on Acuson Siemens SC 2000 and Philips IE 33 devices according to the standard protocol. The visualization was carried out in B-mode with the assessment of the left ventricular end diastolic volume (LV) (LVEDV, ml), left ventricular end systolic volume (LVESV, ml), ejection fraction (EF,%), LV wall thickness (PWT — posterior wall thickness, IVST — interventricular septal thickness , mm), dimension of the left atrium (LA, mm) and the right atrium (RA, mm). Determination of pericardial effusion and systolic pressure in the pulmonary artery (SPPA, mm Hg) were performed. Using pulse-wave tissue Doppler imaging (PW-TDI), peak early diastolic filling (E, cm/s), peak late diastolic filling (A, cm/s), peak ratio E/A, isovolumic relaxation time (IVRT) were estimated. Mitral valve ring velocities were also measured — LV Em (diastolic peak velocity of early diastolic filling during mitral ring movement), LV E/Em (ratio of peaks of early diastolic filling to early diastolic displacement of mitral ring tissues), S (cm/s) — systolic peak. They were evaluated using PW-TDI of the lateral part of the TV ring: peak velocities of RV Em, RV E/Em R, RV S. The averaged echocardiographic parameters of each of the recipients were calculated in the first observation period after the HT, at the time and after the AMR crisis, and at the last observation period.

**2D-STE.** During planned and emergency hospitalizations, with suspected AMR crisis, 2D-STE was performed for cardiac recipients. In the gray scale image, the obtained segments were evaluated using the Acuson Simens SC 2000 device. In order to

**Table 1**

**Parameters of strain and mechanics in the last year of follow-up for 5 groups**

| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 |
|---|---|---|---|---|---|
| LV GLS, %[1] | -15,57±0,59 | -15,66±0,59 | -17,82±1,49 | -15,45±0,46 | -18,26±1,48 |
| RadS LV, %[2] | 30,67±0,99 | 30,55±2,08 | 30,27±2,48 | 29,22±3,97 | 31,10±2,46 |
| CirS LV, %[3] | -22,02±1,96 | -20,09±1,25 | -21,86±2,16 | -21,71±1,83 | -22,69±2,50 |
| ROTAPEX°[4] | 6,41±1,01 | 5,24±0,91 | 6,49±1,16 | 6,68±1,24 | 5,69±1,14 |
| ROTBASE°[5] | -2,39±6,50 | -5,91±1,09 | -6,89±0,92 | -6,23±1,30 | -6,13±1,41 |
| ROTMID°[6] | 2,41±0,87 | 2,88±0,82 | 1,77±0,92 | 2,75±0,81 | 3,21±1,42 |
| TWIST, %[7] | 12,00±1,10 | 11,75±1,04 | 12,97±0,96 | 12,09±1,18 | 11,93±1,94 |
| RV-FWS, %[8] | -18,59±1,03 | -17,11±0,72 | -18,29±1,23 | -17,69±1,07 | -17,86±1,20 |

**Abbreviations:** LV GLS, % — LV global longitudinal strain, [2]LV RadS, % — LV radian systolic strain, [3]CirS LV, % — circular systolic strain, [4]ROTAPEX° — rotation of apical segments, [5]ROTBASE° — rotation of basal segments, [16]ROTMID° — rotation of medial segments, [8]RV GLS, % — RV global systolic strain, group 1 — patients with DSA and AMR crisis, group 2 — patients with non-DSA and AMR crisis, group 3 — patients with HLA AB, without AMR crisis, group 4 — patients with AMR crisis, without identified HLA AB at the time of the study, group 5 — control, patients without AMR crisis and HLA AB.

evaluate global longitudinal strain (LV GLS, %), the apical two-chamber (A2C), three-chamber (A3C) and four-chamber (A4C) positions were used [7]. Radian strain (LV Rad S, %) was determined for the basal area along the short LV axis in the parasternal position. Circular strain (Cir S LV, %) was determined at the level of the basal area along the short LV axis. To assess twisting (twist, %), we used images along the short axis at the base (Rotbase°) and the apex of the LV (Rotapex°). Assessment of the right ventricle free wall strain (RV-FWS) was determined by A4C projection [7].

**Statistical methods.** To describe the clinical parameters, the arithmetic mean was used together with the confidence interval, standard deviation (M±σ), standard error, median with upper (75%) and lower quantiles (25%). To compare the means in more than 2 groups, the Kruskal-Wallis test was used. Comparison of the averages during repeated measurements was carried out using the sign and Wilcoxon tests. When analyzing the degree of correlation between clinical indicators, groups of patients Spearman's rank correlation coefficient was used. Analysis of the relationship structure was conducted using contingency tables in conjunction with the Pearson's chi-squared test, ML (maximum likelihood) Chi-square, F-test, coefficient of contingency, Spearman's correlation coefficient [8]. Kaplan-Meier curves were used to analyze patient survival and the development of AMR. Diagnostic efficacy was assessed by ROC analysis. In order to predict the AMR crisis, an artificial neural network has been built. The architecture of the neural network consists of a two-layer perceptron. The first number indicates the quantity of variables in the network model — input data, the second and third ones — the quantity of hidden and output neurons in the model. The greater the performance, the more accurate the prediction is. The maximum possible performance is 100%.

Statistical processing was conducted by STATISTICA 10 (Tibco, USA) software.

## Results

According to endomyocardial biopsy data, out of 132 recipients, 28 patients (21,2%) showed signs of AMR in accordance with the criteria for working formulations of the International Society for Heart and Lung Transplantation (WF-ISHLT from 2005 and revision from 2015). Among patients with AMR crisis — 57% were dead, without AMR crisis — 14% were dead. The largest percentage of deaths in group 1 was 60%, followed by group 2 — 57%, group 4 — 55%. Group 5 (without HLA AB, signs of AMR and cell rejection) had only 17% of deaths, in group 3 there were no deaths.

At the first stage, the heart recipients underwent dynamic TTE observation. First, an estimate of the arithmetic mean and standard error (standard deviation divided by the sample size) was determined for the TTE parameters in the first year of observation, then at the time of the AMR crisis and the last observation period. Intergroup differences in the parameters of the first observation year, using the Kruskal-

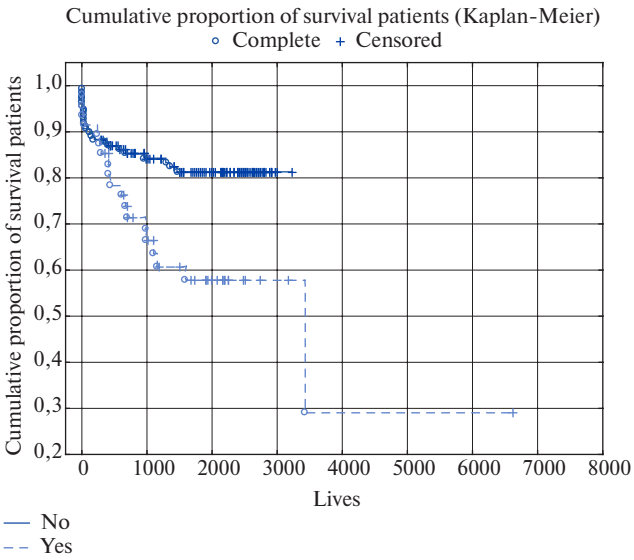


**Fig. 1.** AMR risks for patients with and without HLA AB.

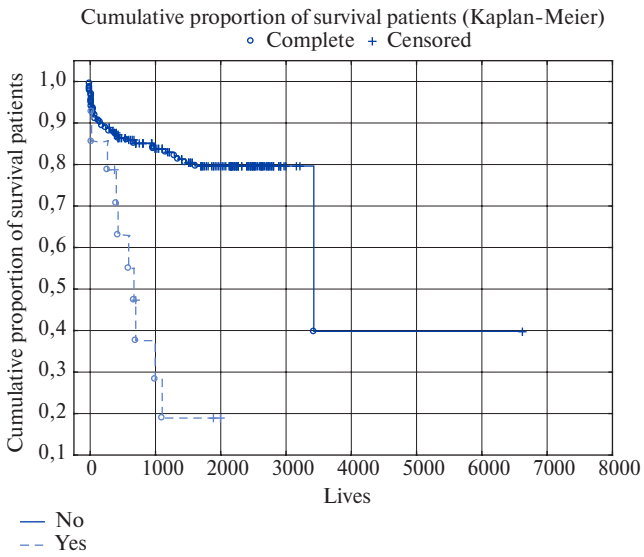


**Fig. 2.** The risks of AMR for recipients with and without DSA.

Wallis test, revealed the homogeneity of the five studied groups in almost all parameters ($p<0.05$). Group 5 includes recipients who did not have episodes of AMR and cell rejection during the observation period. Thus, TTE parameters of group 5 correspond to the standard values of heart transplant recipients. Groups 1, 2, 4 included recipients, who had AMR crisis. The intergroup differences of the last observation year revealed the statistical significance of the averages for 14 parameters ($p<0,05$), for 7 parameters there were no statistically significant changes ($p>0,05$). So, in group 1, when comparing the parameters of the first and last observation years, the following statistically significant changes can be noted: change in LV dimension ($p=0,004$), IVST ($p=0,045$), PWT ($p=0,026$), E/A ($p=0,036$), LV S ($p=0,012$), RV S ($p=0,004$), SPPA ($p=0,004$), RA ($p=0,004$), $p <0,05$. In group 2, differences were noted: LA ($p=0,023$), IVST ($p=0,023$), PWT ($p=0,041$), E/A ($p=0,023$), RV S ($p=0,023$), SPPA ($p=0,023$). In group 4, there were following changes: LA ($p=0,015$), LV end-diastolic dimension (EDD) ($p=0,045$), IVST ($p=0,044$), PWT ($p=0,002$), A ($p=0,026$), LV E/Em ($p=0,036$), SPPA ($p=0,045$), RA ($p=0,045$), IVRT ($p=0,026$), DT ($p=0,026$).

In order to identify AMR predictors, a correlation analysis was performed for the parameters of the standard TTE, which showed a statistically significant ($p<0,05$) difference in the crisis groups for LA, LV EDD, IVST, RV and EF. All parameters with statistically significant correlations can be used as predictors in models.

At the second stage, recipients were examined using the 2D-STE technique. First, the arithmetic and standard errors were estimated for the parameters of strain and mechanics in the first observation period, then at the time of the AMR crisis and the last observation period. The results of group 5 correspond to the normative values of heart transplant recipients without crisis. The Kruskal-Wallis test did not reveal a statistically significant difference in average values of the parameters in the groups for the first year of observation ($p>0,05$).

At the time of the AMR crisis, significant changes in the strain parameters and mechanics were revealed: LV GLS was 9,94±1,37%, LV Rad S — 19,36±3,66%, LV Cir S — 17,83±4,89, ROTAPEX° — 4,51±1,46, ROTBASE° — 4,75±2,12, ROTMID° — 1,94±1,41, TWIST — 8,90±1,85%, RV-FWS — 15,89±0,89%.

The possible diagnostic criteria for AMR crisis were: global peak systolic strain, sensitivity (Se) 86,2%, specificity (Sp) — 90,4%; radian systolic strain, Se — 75,8%, Sp — 84,5%; circular systolic strain, Se — 78,6%, Sp — 84,4%; LV twisting, Se — 66,7%, Sp — 94,2%, $p<0,001$, When LV GLS and the longitudinal peak strain of the right ventricle are taken into account, Se increases to 91,9%, Sp to 94,6%, and $p<0,001$ in the diagnosis of AMR crisis.

Table 1 presents the parameters of strain and mechanics in 7 years' follow-up. Patients of groups 1, 2 and 4 at this point had an AMR crisis. In group 1, a change was found in the following parameters: LV GLS ($p=0,004$), ROTBASE ($p=0,045$). In group 2, there were statistically significant changes: LV GLS

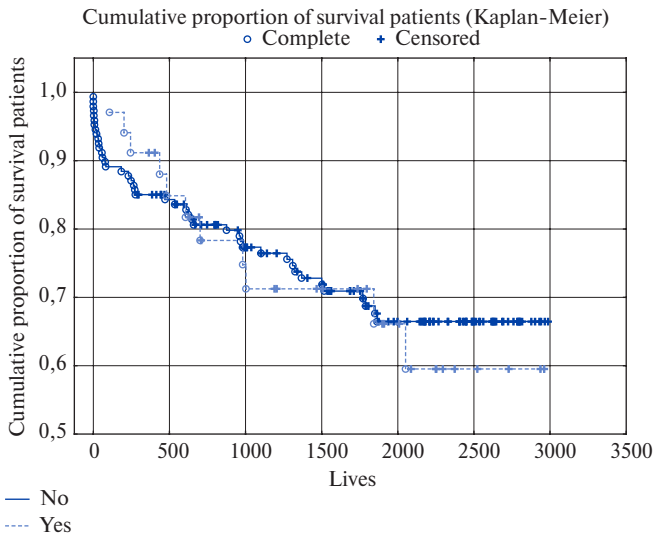


**Fig. 3.** Survival of patients with identified HLA AB *de novo*.

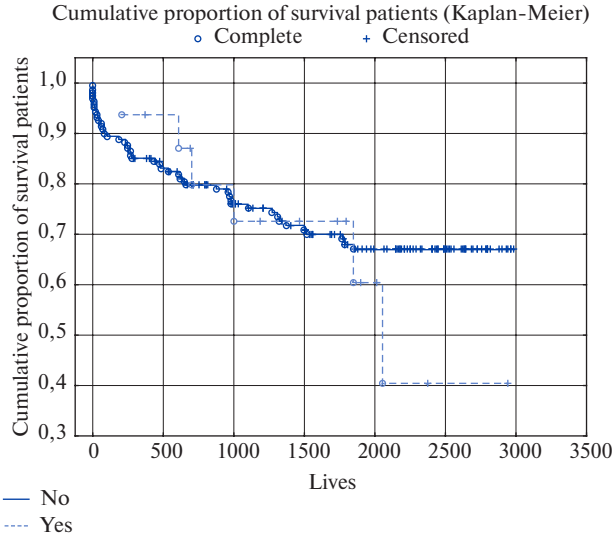


**Fig. 4.** Survival of patients with identified DSA *de novo*.
**Abbreviation:** DSA — donor-specific antibodies.

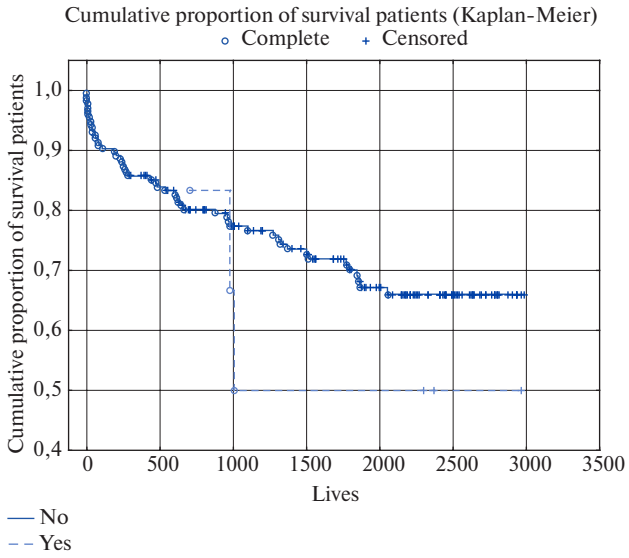


**Fig. 5.** Survival of patients with identified AB in the late period after HT.

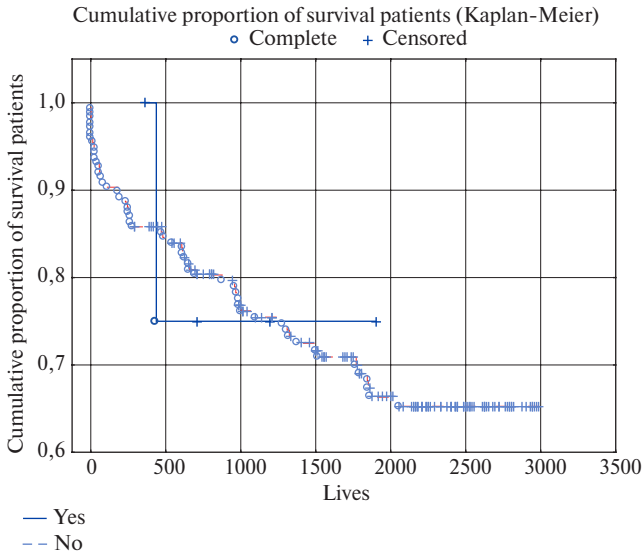


**Fig. 6.** Survival of patients with identified AB in the early period after HT.

(p=0,023), LV Rad S (p=0,042), LV Cir S (p=0,023); in group 4 — LV GLS (p=0,015), Rad S LV (p=0,046).

Patients with a history of AMR crisis had a statistically significant change in the following parameters: LV GLS, LV Rad S, LV Cir S. These indicators can be good predictors of an adequate prediction model for AMR crisis.

Further, the analysis of recipients with identified *de novo* HLA AB at different times after HT was performed. An assessment of the survival of recipients with HLA AB in the early and late posttransplant period, risk of transplant coronary artery disease (TCAD), a comparative characteristic of survival in patients with the AMR crisis and cell rejection.

Of the 34 recipients with HLA AB, DSA was identified in 16 (47,06%), 18 (52,94%) recipients had non-DSA.

Using Spearman's rank correlations, statistically significant (p<0,05), moderate associations between DSA and AMR crisis (rs=0,325) were revealed. We identified weak associations between DSA and TCAD (rs=0,224), weak associations between DSA and cell rejection crisis (rs=0,162).

The next stage, in order to assess the survival of heart recipients with identified HLA AB and prob-

ability of the recipient living for more than the specified period of time without AMR crisis and other complications of the posttransplant period, Kaplan-Meier survival curves were applied. We consider the development of a crisis or other complication as a complete event, no development — as censored event. Therefore, AMR risk (TCAD, cell rejection) will be called the probability that the patient could live longer than the specified time without this event.

To identify the risk of AMR developing in patients with HLA AB, Kaplan-Meier survival curves were constructed (Fig. 1). In patients with *de novo* HLA AB, the probability to live without an AMR crisis for more than 5 years, or rather 3,500 days, is only 29%. In the first 1000 days after HT, the survival curve decreases rapidly and from 1500 days to 3400 days, the curve stabilizes, and from 3400 days the risk of AMR sharply increases. At the same time, the probability of patients without HLA AB to live more than 3000 days without an AMR crisis is higher and equal to 80%. Figure 2 shows the ability to live longer than the specified time period without an AMR crisis in patients with *de novo* DSA and without DSA. It is seen that the risk of AMR crisis in patients with DSA is even higher than for patients with HLA AB *de novo*. The probability of living without AMR for more than 1000 days is only 0,19. That is, only 19% of recipients have a chance to live without AMR for more than 1000 days. At the same time, the risk of AMR in patients without DSA is much lower, so the probability of living more than 1,500 days is 80%, and the probability of living more than 3,400 days is 40%.

Analysis of the Kaplan-Meier curves for patients with DSA and other complications of the posttransplant period showed that the risk of cell rejection and TCAD in patients with DSA is lower compared to AMR. So, 78% of recipients are able to live without cell rejection for more than 1000 days, 62% can live more than 1800 days without TCAD. Figure 3 shows the survival graphs of recipients with and without HLA AB. Until 2000 days, survival is about the same. But, for a period of more than 2000 days, the survival rate of patients with HLA AB (59%) is lower than in patients without it (66%).

Survival of patients with and without DSA is shown in Figure 4. The graph shows that the probability of surviving more than 2000 days for patients with DSA is lower and equal to 40%, compared with patients without circulating DSA, in which the survival rate is 68%.

For a comparative analysis of the survival of patients with identified antibodies in the late period (three or more years after HT) and patients without HLA AB, Kaplan-Meier curves were constructed (Figure 5). The graph shows a sharp decrease in the survival curve after 1000 days for patients with antibodies detected in the late period. At the same time, the probability of surviving more than 1000 days for patients with HLA AB is 50%, for patients without HLA AB this probability is significantly higher and equal to 78%. In patients without HLA AB, there is a gradual decrease in survival function and by 6800 days is 68%, which is higher than survival rate in the same period of patients with HLA AB — 50%.

Figure 6, which shows the survival of patients with HLA AB that appeared in the early period (first month after HT), and without HLA AB, shows that the survival curve of patients with HLA AB, after about 300 days, sharply decreases by 400 days and reaches 75%. For patients without HLA AB, by 400 days there is a higher survival rate — approximately 85% of patients can live more than 400 days after HT, but overall, with an increase in the number of days lived, the survival rate decreases and reaches 65% by 1800 days, from 2000 days the survival rate stabilizes by level of 50%.

Thus, a comparison of the survival of patients with identified antibodies at different time periods after HT showed that HLA AB in the late period after HT lead to worse survival of recipients — 50%, compared with antibodies in recipients in the early posttransplant period — 75%

**Neural network.** Identified predictors can be used in the construction of an artificial neural network to determine the AMR risk. The program generated about 400 networks, from which a network with the best predictive efficiency was selected. The architecture of the two-layer perceptron consists of three layers. The first indicates the number of variables in the network model — 14, corresponds to the input parameters: eight quantitative — LV GLS, LV Rad S, LV Cir S, RV GLS, LV EDD, IVST, EF, RV and three qualitative parameters — DSA, non-DSA, HLA AB. Each can take on two values (yes, no), all in all qualitative variables take on 6 values. The intermediate layer contains 16 elements. On the last layer there are 2 neurons (yes, no) that predict the risk of AMR crisis. The fractions of correctly classified patients in the training, control and test samples took on the highest values — 100%, 100%, 89,47%, therefore we can consider the network acceptable for solving the problem of predicting the risk of AMR crisis. The total predictive capability of the network is 98,49%

## Discussion

The study showed a low survival rate for patients with *de novo* HLA AB, especially with DSA — 40%, compared with recipients without DSA — 68%, which is comparable with data from other researchers. Smith JD, et al. performed a retrospective analysis of a group of recipients with *de novo* DSA and revealed low recipient survival (HR=3,198), which is comparable with the results of our study [9]. Similarly, by examining the survival of cardiac recipients with DSA, Coutance G, et al. found that 15-year survival was highest among recipients without DSA compared with those who identified DSA (70% versus 47%). Therefore, the screening and identification of HLA AB, in particular, *de novo* DSA, provides the most comprehensive information for the clinical observation of recipients with risk of AMR [10, 11].

The values of strain and heart mechanics in our study coincide with the normative range in healthy patients presented by the European Association of Echocardiography (EAE) [12, 13]. It was shown that AMR crisis in patients with and without antibodies to HLA, global peak systolic strain (-9,94±1,37%) can be used as predictor; Se — 86.2%; Sp — 90.4% radian systolic strain (19,36±3,66%); Se — 75,8%; Sp — 84,5%; circular systolic strain (-17,83±4,79%); Se — 78,6%; Sp — 84,4%, global stein of the right ventricle (-15,89±0,89%) at $p<0,001$. When LV GLS and longitudinal global strain of the right ventricle are taken into account, Se increases to 91,9%, Sp — to 94,6% ($p<0,001$) in the diagnostics of AMR.

Having carried out a multivariate analysis of the TTE parameters in the first observation period and before the development of severe rejection crisis, we were able to identify the predictors of the severe AMR; statistically significant changes at $p<0,05$ [14] were revealed for the parameters of LV EDD, LV IVST, EF and RV. Changes are most significant in patients with DSA.

The present study showed the relationship between changes in the parameters of strain and the mechanics of the heart transplant, parameters of TTE (volume of the left and right ventricles, ejection fraction, thickness of the interventricular septum) and immunopathological data, such as detection of HLA AB.

## Conclusion

Screening and identification of *de novo* DSA with the aim of risk assessing and monitoring of AMR, provides the most comprehensive information for the clinical observation of heart recipients. Identified late HLA AB lead to AMR crisis and a decrease in survival.

A neural network model for determining the risk of AMR including the TTE predictors, 2D-STE, posttransplant HLA AB, age and gender of the recipient (the fractions of correctly classified patients took on the highest values — 100%, 100%, 89,47%). The total predictive capability of the network is 98,49%. A neural network may be acceptable for solving the problem of predicting the risk of AMR crisis.

**Conflicts of Interest:** nothing to declare.

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# Analysis of the neuronal damage severity and cognitive status in patients after operations on the aortic arch

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**Aim.** To assess the neuronal damage severity and cognitive status in conditions of unilateral antegrade cerebral perfusion through the brachiocephalic trunk during surgical reconstruction of the thoracic aorta.

**Material and methods.** The study included 144 patients with aneurysm and dissection of the thoracic aorta. Patients underwent reconstructive surgery under cardiopulmonary bypass, unilateral antegrade cerebral perfusion and circulatory arrest. Before and after the intervention, a cognitive status analysis was performed using the Montreal Cognitive Assessment (MoCA), Amatinu test and Schulte tables. The dynamics of neuron-specific enolase (NSE), a marker of neuronal damage, was determined perioperatively.

**Results.** The duration of cardiopulmonary bypass was 155 [115; 201] min, cardioplegic arrest — 100 [72; 150] min, unilateral perfusion — 20 [15; 51] min, circulatory arrest — 20 [15; 30] min. Hospital mortality was 7% (10 cases). Neurological complications were noted in 12 (8%) cases. All patients in the postoperative period (within 24 hours) showed an increase in NSE compared with baseline values (3,3 μg/L and 2,07 μg/L, respectively, p=0,0003), but not exceeding the upper limit of normal (9,9 μg/l). According to the results of psychometric tests, which were carried out upon admission to the hospital and 2 weeks after the operation, there were no negative changes (MoCA test: 24 [21; 26] points — 26 [24; 27] points, p=0,00001; Schulte tables: 288 [240; 368] s — 278 [241; 328] s, p=0,01; Amatuni sample 264 [216; 297] s — 254 [221; 280] s, p=0,57).

**Conclusion.** Based on the analysis of the perioperative dynamics of neuronspecific enolase and cognitive tests, unilateral cerebral perfusion through the brachiocephalic trunk is effective and relatively safe. This method of perfusion protection of the brain helps to minimize postoperative neurological complications during operations on the thoracic aorta.

**Key words:** thoracic aorta, antegrade unilateral cerebral perfusion, circulatory arrest, neuron-specific enolase (NSE), cognitive dysfunction, neurological complications.

**Conflicts of Interest:** nothing to declare.

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Surgical treatment of diseases of the thoracic aorta is a modern urgent problem in cardiac surgery and cardiothoracic anesthesiology. These operations are characterized by large injury and require not only the use of cardiopulmonary bypass (CPB), but also the perfusion and anesthetic protection of the brain. For a long period of time, deep hypothermia without cerebral perfusion was the main method of cerebral protection [1]. Later, various options for perfusion cerebral protection were proposed: bilateral, unilateral antegrade and retrograde perfusion [2].

Most often, the assessment of the effectiveness of various types of perfusion protection of the brain is currently based on various intraoperative instrumental tests (infrared spectroscopy, transcranial dopplerography, electroencephalography), which are mainly indirect. At the same time, laboratory and clinical diagnostics of neurological disorders in the postoperative period is more specific, but it has not been studied enough.

Ain of the study was to assess neuronal damage and cognitive status in conditions of unilateral antegrade cerebral perfusion (ACP) through the brachiocephalic trunk (BCT) during surgical reconstruction of the thoracic aorta.

## Material and methods

In the period from August 2008 to April 2018, 144 reconstructions of the thoracic aorta under the conditions of CPB, circulatory arrest (CA) and unilateral ACP through BCT were performed at Tomsk National Research Medical Center. Patient characteristics are presented in Table 1.

Most operations were performed due to aneurysms of the thoracic aorta, and in 31% due to dissection. The most frequently performed prosthetics of the aortic arch were the hemiarch replacement (65%) and the reconstruction of the thoracic aorta using the frozen elephant trunk technology (33%).

In addition to the intervention on the thoracic aorta, 72 (50%) patients required combined operations for concomitant cardiac pathology, including: aortic valve prosthetics — 46 (32%), aortic root replacement according to techniques of T. David — 5 (3%) and Bentall DeBono — 8 (6%), coronary bypass surgery — 14 (10%) patients, mitral valve prosthetics — 1 (0,7%).

To carry out perfusion cerebral protection, an original technique was used to connect the arterial line of the CPB circuit through prosthesis which end-to-side sewn in the BCT [3].

Anaesthetic support was performed as combined anesthesia. Premedication was performed with a narcotic analgesic, benzodiazepine and antihistamine. Induction into anesthesia was performed with fentanyl (3,0-5.0 μg/kg) and propofol (1,5 mg/kg). Pipecuronium bromide (0,1 mg/kg) was used to provide myoplegia. Sevoflurane inhalation (2-3 vol%) was used to maintain anesthesia before and after CPB; propofol infusion (4,0-5,0 mg/kg) was used during perfusion. Analgesia was maintained by fentanyl infusion (3-5 μg/kg/h).

CPB was performed on an S3 console (Stockert, Germany) using Skipper oxygenators (Eurosets, Italy). The perfusion volumetric rate was 2.5 L/min/$m^2$. At the CA stage, the volume of unilateral ACP was 8-10 ml/kg/min, while the pressure in the arterial line was maintained in the range of 60-80 mm Hg. To ensure hypocoagulation prior to CPB, heparin was administered at a dose of 3 mg/kg while maintaining an activated clotting time >480 s. For myocardial protection, cold crystalloid cardioplegia was used (Custodiol, Koehler Chemi, Alsbach-Haenlien, Germany). After perfusion, the effect of heparin was neutralized by the introduction of protamine sulfate in a 1:2ratio.

At all stages of operations, an electrocardiogram (ECG) was monitored, invasive blood pressure monitoring in both radial arteries using a 20G arterial cannula (B Braun, Germany), central venous pressure (CVP) using a 12F central venous catheter (Certofix, B Braun, Germany), nasopharyngeal and rectal temperatures were recorded using an Infinity® Delta XL apparatus (Dräger, Germany). We also analyzed the gas, acid-base and electrolyte composition of arterial blood. Catheterization of the bladder was performed to control hourly urine output. Artificial lung ventilation (ALV) was performed on a Primus apparatus (Dräger, Germany).

In addition, cerebral oximetry ($rSO_2$,%) of the right and left hemispheres was monitored using infrared spectroscopy (INVOS 5100, Somanetics, USA). $RSO_2$ indices were analyzed at the stages of induction of anesthesia, during CPB before CA, during CA, when warming before CPB weaning, at the end of the operation.

In the blood serum, the level of a marker of neuronal damage, neuron-specific enolase (NSE), was determined by enzyme-linked immunosorbent assay. Venous blood sampling for the study was carried out at two points: the main one in the operating room, after venous access, and the control — at the next morning after the operation. For the study, serum was used, which was centrifuged for 10 minutes. The NSE level of 9,9 μg/L was considered the upper normal limit, the median — 6,5 μg/kg.

**Table 1**

**Clinical and demographic characteristics of patients**

| Parameter | n |
|---|---|
| Age, years | 56±12 |
| Males, n (%) | 97 (67) |
| Type of aortic pathology | |
| Aneurysm of the ascending aorta, n (%) | 92 (64) |
| Aneurysm of the aortic arch, n (%) | 6 (4) |
| Aneurysm of the descending aorta, n (%) | 7 (5) |
| Stanford type A aortic dissection, n (%) | 24 (17) |
| Stanford type B aortic dissection, n (%) | 15 (10) |
| Comorbidity | |
| Hypertension, n (%) | 114 (80) |
| Diabetes mellitus, n (%) | 8 (6) |
| Acute cerebrovascular accident, n (%) | 6 (4) |
| Chronic cerebral ischemia, n (%) | 9 (6) |
| Atrial fibrillation, n (%) | 20 (14) |

**Table 2**

**Intraoperative parameters**

| Parameters | Result |
|---|---|
| Operation time, min | 325 [260; 405] |
| CPB time, min | 155 [115; 201] |
| Cardiac arrest time, min | 100 [72; 150] |
| ACP time, min | 20 [15; 51] |
| CA time, min | 20 [15; 30] |
| Moderate hypothermia (25-28°C), n | 144 |

**Notet:** data are presented as Me [25; 75**]**.
**Abbreviations:** CPB — cardiopulmonary bypass, ACP — antegrade cerebral perfusion, CA — circulatory arrest.

Upon admission to the hospital (source data) and after 2 weeks of surgery patients underwent psychometric tests. We used the following tests: Montreal Cognitive Assessment (MoCA test), correction task (Amatuni test), Schulte tables. The methodology is presented in the Annex.

Statistical analysis of the data was carried out in STATISTICA 13,3 (StatSoft.Inc., USA) software. The normality of indicators' distribution was verified using the Kolmogorov-Smirnov test. Quantitative values were expressed as mean±standard deviation (M±SD) under normal law of distribution. With an unknown distribution law, the data were presented as the median and 25-75 percentiles (Me [25; 75]). In normal distribution, t-test was used for independent and dependent samples. Comparison of quantitative characteristics with an unknown data distribution was carried out using the Mann-Whitney U-test, Wilcoxon signed-rank test. Qualitative differences between groups in terms of quality were evaluated using Fisher's exact test. Differences were considered as statistically significant at $p<0,05$.

## Results

The data of the intraoperative period are presented in Table 2. The initial values of cerebral oximetry against the background of normal gas composition of arterial blood, as well as at the main stage and CA were within the reference values with interhemispheric asymmetry of not more than 3% (Fig. 1).

In the postoperative period, the time spent by patients in the intensive care unit was 3 [2; 9] days. The duration of AVL was 21 [12; 55] h. In connection with respiratory failure, tracheostomy for 3-4 days required in 23 (16%) patients. The duration of AVL in patients of this subgroup was 380 [240; 528] hours.

In total, neurological complications were noted in 12 (8%) cases. In 2 (1,4%) patients, in the early postoperative period, there was signs of acute ischemic cerebrovascular accident, 2 (1,4%) — transient ischemic attack, which stopped within 12 hours without residual focal neurological deficit. In 8 (5%) patients — postoperative delirium was without residual effects.

All patients in the postoperative period (within 24 hours) showed NSE increase in compared with baseline values (p=0,0003), but not exceeding the upper limit of normal (Fig. 2).

According to the MoCA test, in patients after surgery there is a statistically significant increase in the total score to 26 [24; 27] (p=0,00001). There was also a statistically significant increase in the indicators of visual-constructive skills — combining numbers and letters, copying a cube and clock-drawing test. According to the results of the Schulte table test there is a statistically significant decrease in the total time of passing the test (p=0,01). According to the correction task, the attention and psychomotor speed of the patients did not change. Initial and postoperative indicators of psychometric tests are presented in Table 3.

The overall hospital mortality rate was 7% (10 cases). The causes of death were: acute intraoperative myocardial infarction (n=4); multiple organ failure,

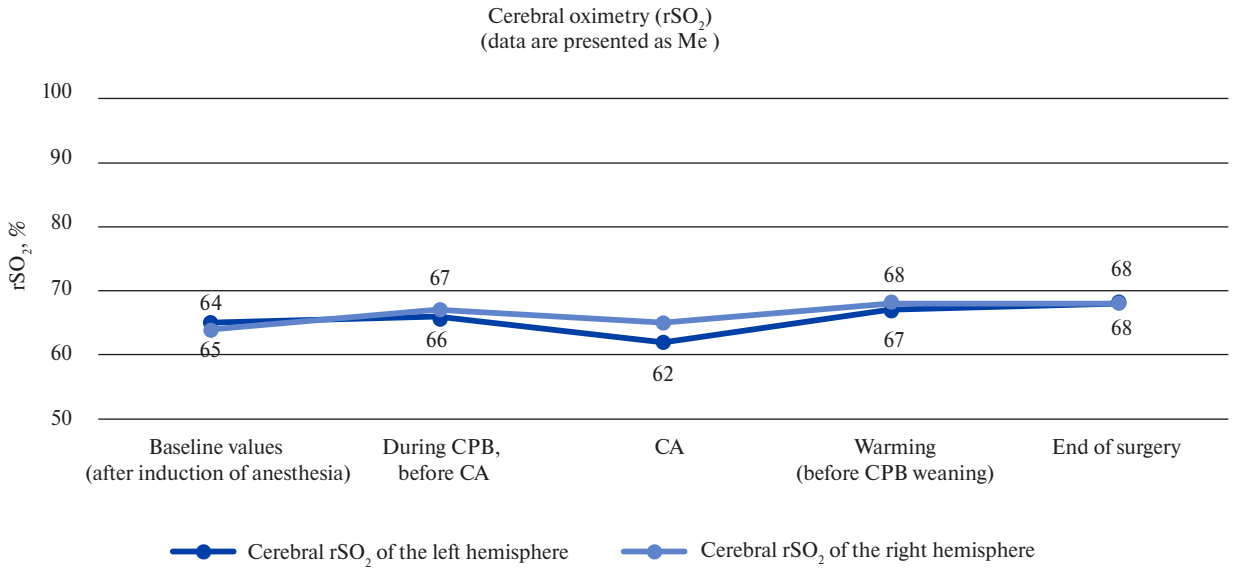


**Fig. 1.** Parameters of cerebral oximetry ($rSO_2$) at different surgery stages.

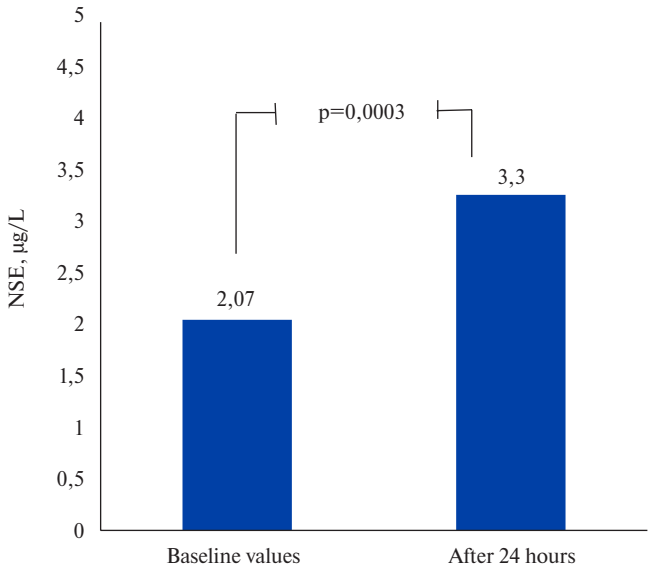


**Fig. 2.** Perioperative changes of serum NSE level.
**Note:** data are presented as Me [25; 75**].**

sepsis (n=5); hemorrhagic shock, DIC (n=1).

## Discussion

Currently, there is no unified approach to the choice of the protecting cerebral method during operations on the aortic arch. Deep hypothermia as a cerebral protection in the reconstruction of the thoracic aorta has fewer supporters. That is because along with the low efficiency of cerebral protection, it is associated with the development of coagulopathy, endothelial dysfunction of the cerebral microvasculature, damage to neurons, an increase in the systemic inflammatory response and an increased risk of organ and systems dysfunctions [4, 5].

Numata S, et al. [6] carried out a comparative analysis of various temperature regimes during operations on the thoracic aorta. It was shown that an admissible protection of the brain and internal organs is provided at a patient's body temperature of more than 28°C. The advantage of moderate hypothermia is associated not only with the hypothermic effect, but also with the reduction in the time required for cooling and warming the patient. In turn, it determines the duration of the CPB as independent risk factor for postoperative central nervous system dysfunction.

Recently, the number of publications has been growing, proving the advantage of ACP over the retrograde variant. So, Okita Y, et al. [7] analyzed the data of interventions on the aortic arch of 8169 patients. It was found that retrograde perfusion is accompanied by a greater mortality and frequency of acute cerebrovascular accident compared with antegrade cerebral perfusion protection. The results obtained by the authors are consistent with the meta-analysis by Tian DH, et al. [5].

Thus, with prolonged and complex interventions on the aortic arch, it is advisable to use ACP [2].

However, the question of choosing the ACP variant remains open. So, Malvidi P, et al. [8], analyzing the data of 3500 operated patients, consider bilateral perfusion as the safest method of cerebral protection.

**Table 3**

**Psychometric test results**

| Тест | Before surgery | After surgery | p-value |
|---|---|---|---|
| MoCA test, score | 24 [21; 26] | 26 [24; 27] | p=0,00001 |
| Visual-constructive skills, score | 4 [3; 5] | 5 [4; 5] | p=0,005 |
| Schulte table (total time), sec | 288 [240; 368] | 278 [241; 328] | p=0,01 |
| Amatuni test (total time), sec | 264 [216; 297] | 254 [221; 280] | p=0,57 |
| Amatuni test (fatigue index) | 1,09 [0,98; 1,19] | 1,10 [1,03; 1,21] | p=0,376 |

**Note:** data are presented as Me [25; 75**].**

In addition, some researchers believe that with an increase in stopping blood circulation for more than 40-50 minutes, it is justified to use bilateral perfusion [9]. It is assumed that this method of neuroprotection has advantages over unilateral one in cases of anomalies of the Willis circle and history of strokes [8].

Angeloni E, et al. [10] presented data from a meta-analysis of 5100 patients operated on the aortic arch using both cerebral perfusion techniques. It was shown that unilateral and bilaterial perfusion are accompanied by a comparable frequency of persistent neurological deficit (6,1% versus 6,5%; p=0,8), while transient cerebrovascular accidents were recorded more often with bilateral cerebral perfusion (7,1% against 8,8%; p=0,46). Mortality in the groups did not statistically differ (8,6% versus 9,2%; p=0,78). A higher frequency of neurological deficit in the group of patients with bilateral perfusion is associated with additional manipulations on the modified supra-aortic arteries, which increases the risk of material embolism.

A number of studies have shown that unilateral ACP has an advantage in terms of early survival and postoperative persistent neurological complications. It is important to note that the frequency of permanent neurological complications in bilateral perfusion is 1,6-9,8% [11], and in unilateral — 1,1-4,2% [12].

In the prevention of cerebral complications, along with the cerebral perfusion, its duration is of great importance. So, according to the literature, the duration of cerebral perfusion for more than 40 minutes is associated with postoperative neurological deficit. An increase in its duration to 65 min or more is associated with an extremely high mortality rate [13, 14]. Our study also noted a tendency to increase in neurological complications with increasing cerebral perfusion time.

To date, the assessment of the effectiveness of perfusion cerebral protection is mainly based on data from instrumental methods such as infrared spectroscopy, transcranial Doppler, and electroencephalography. However, such an analysis is more indirect. For more accurate intraoperative monitoring of neurological status, an analysis of neuron-specific markers, S100, S100B, and NSE proteins, was proposed [15, 16]. It has been empirically established that the most reliable and specific indicator reflecting cerebral injuries during surgical interventions, as well as postoperative neuropsychological disorders, is the NSE [17, 18]. According to the results of our study, all patients in the postoperative period (within 24 hours) showed an increase in NSE compared with baseline values (p=0,0003), but not exceeding the upper limit of normal. Neurological complications were noted in 8% of cases, but only 1,4% of patients had a persistent neurological deficit. Thus, unilateral cerebral perfusion through BCT provides adequate cerebral protection.

In addition to neurological complications, much attention is paid to the problem of postoperative cognitive dysfunctions (POCD), which, being a milder manifestation of neurological disorders, lead to a significant deterioration in the quality of life of patients [19]. A generally accepted definition and clear diagnostic criteria for POCD have not yet been developed; their clinical manifestations are impaired attention, memory, speech, and other cognitive functions, often diagnosed using neuropsychological testing [20-23].

An analysis of our own data showed that reconstructive surgery on the aorta does not adversely affect cognitive functions, but even vice versa, leads to an improvement in counting, praxis, neurodynamic functions, attention and concentration skills, which is confirmed by an increase in the total score of the MoCA test after surgery. The operated patients showed a statistically significant increase in the indices of visual-

constructive skills — combining numbers and letters, copying a cube and the clock-drawing test. According to the results of the Schulte table test, a reduction in the time spent for passing the test was noted, which indicates improved stability and attention, increased work efficiency, warming-up, psychological stability. Improvement in cognitive functions appears to be associated with improved cerebral blood supply, as well as a decrease in hypoxia after surgery.

## Conclusion

Based on an analysis of the perioperative changes of NSE and cognitive tests, unilateral cerebral perfusion through BCT is effective and relatively safe. This method of perfusion cerebral protection helps to minimize postoperative neurological complications during operations on the thoracic aorta.

**Conflicts of Interest:** noting to declare.

## Annex

**Montreal Cognitive Assessment (MoCA)** is used for assessing of various cognitive skills: attention and concentration, executive functions, memory, speech, visual-constructive skills, abstract thinking, counting and orientation. The time for holding is approximately 10 minutes. The maximum possible score is 30; 26 points or more is considered as normal.

**Correction task** is a method of stability and attention focusing studying. The patient is provided with a correction task form, which presents numbers from 0 to 9 in random order. Patient is invited to look at these numbers line by line, from left to right, and cross out “6” and “9”. After the test is completed, the task is checked for correctness according to a special “key”. The total number of errors is analyzed, as well as the number of errors made in the first and second half of the table.

**Schulte table** determine attention span and changes of performance. The test subject is offered five tables in turn, on which the numbers from 1 to 25 are arranged in random order. The test subject seeks for, shows and names the numbers in ascending order. The total test time is estimated and the average value for each square is calculated.

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# Delayed help-seeking for emergency medical care of patients with acute coronary syndrome/myocardial infarction: review of studies

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The review article provides an analysis of domestic and foreign studies evaluating the dynamics of temporary indicators of prehospital medical care for patients with acute coronary syndrome (ACS)/myocardial infarction (MI). It was noted that the delay in applying for medical care of patients with ACS/MI is currently a significant factor determining the effectiveness of the treatment of these diseases. Over the past decades, modern treatment methods and bright-line health system recommendations have appeared. Significant progress has been made in reducing the time from calling an ambulance to receiving treatment, especially in developed countries. However, in spite of the efforts made, the problem of late appealability of patients is still unresolved. In the world and in Russia, experience aimed to educate patients in terms of ACS/MI symptoms and the importance of timely help-seeking has been gained at the population level. There is no doubt that along with organizational measures aimed to treat cardiovascular patients, increasing public awareness of the ACS symptoms and emergency aid should be considered as one of the priority areas.

**Key words:** acute coronary syndrome, acute myocardial infarction, risk factors, delayed help-seeking.

**Conflicts of Interest:** nothing to declare.

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Cardiovascular diseases (CVD) remain one of the leading causes of high mortality in the Russian Federation (RF) [1]. Since 2003, in Russia there has been a steady downward trend in CVD mortality, amounting to 616,4 deaths per 100 thousand people in 2016 [2].

Nevertheless, the standardized CVD mortality rates in the Russian Federation when compared with most European countries remain still high (647,6 for men and 345,1 for women) [2, 3]. At the same time, coronary artery disease (CAD) makes the largest contribution to the CVD mortality, and mortality rate from myocardial infarction (MI), in 2016 amounted to 42,9 cases per 100 thousand people [2].

CAD is the main component in economic CVD damage (39,6%) in 2016, which amounted to more than 1 trillion rubles. In turn, MI accounted for more than 213,2 billion rubles. [4] But despite all the successes and achievements of recent years associated with the active introduction of modern methods of reperfusion therapy and more frequent use of drugs that prevent CAD progression, the problem of providing medical care (MC) to patients with MI remains global in our country [1, 4]. So, for example, according to the Monitoring of the Ministry of Health of Russia, hospital mortality in acute coronary syndrome (ACS) in 2016 amounted to 13,8% [5], which, unfortunately, is 2 times higher compared to European countries [3].

It is known that mortality from myocardial infarction is determined by a complex of causes depending both on the patient and on the healthcare system. And if today it has been possible to achieve some positive results, mainly due to minimizing time spending at the system level [6, 7], then with regard to the patient-related period, the target time has not yet been established (Fig. 1). It is believed that reducing the time at this stage of primary health care can significantly reduce the mortality rate from acute MI [8, 9].

In this regard, it is of particular interest to analyze the factors that influence a patient with ACS/IM making a decision to seek for MC.

**Delays in seeking for MC according to foreign studies**

Long-term trends in the interval from the onset of MI symptoms to hospitalization were studied in an American observational study, which included more than 5967 patients with acute MI, from 1986 to 2005 [10]. When analyzing the data, approximately 45% of patients were hospitalized within the first 2 hours of the onset of symptoms of the disease, 34% were hospitalized 2-6 hours after the onset of symptoms, and 21% 6 or more hours after the onset of symptoms. It was shown that the average value and the median of the time of pre-hospital delay were 3,6 and 2 hours in 1986, 3,9 and 2 hours in 1995 and 3,7 and 2 hours in 2005. Thus, over the 20-year period of the study, the time of pre-hospital delay in most patients did not change significantly.

In a randomized multicenter study (893 patients), conducted in Ireland in 2007-2009, the average time from the onset of symptoms of ACS to the hospitalization ranged from 1,5 to 6 hours [11]. A feature of this study was that the delay time in ACS at the pre-hospital stage was largely determined by pain syndrome severity. In particular, patients with a moderate pain syndrome with the development of ACS took an average of 1,5 hours more time to come to the hospital.

According to McKee G, et al. (2013), the average value of the delay time at the pre-hospital stage in patients with ACS was 4,06 h, and in patients with ST elevation MI (STEMI) and non-ST elevation myocardial infarction (non-STEMI) — 2,7 h and 4,51 hours, respectively [12]. A multivariate analysis revealed that in the subgroups of patients with MI, oligosymptomatic or asymptomatic MI course is associated with a longer delay in the pre-hospital phase.

Similar data are provided by Nilsson G, et al. (2016) in study performed in Sweden [13]. According to results, the median of the total time of pre-hospital delay in patients with MI was 5.1 hours. Moreover, the majority of the delay was from the onset of the symptoms to sought treatment, which amounted to 3,1 hours, in turn, the transportation time — 1,2 hours,

The formation of a modern system for MC organizing during ACS/MI in developed countries has made it possible to achieve a significant reduction in the "systemic" time delay at the pre-hospital stage. Thus, according to the Austrian study Vienna STEMI Registry (1053 patients), conducted from 2002 to 2004, it was noted that the average time from the onset of symptoms of STEMI to arrival in the hospital was 180 minutes [14]. But, at the same time, the main time for pre-hospital delay was still in the period from the onset of the symptoms to sought treatment (approximately 120±15 min).

In a large-scale observational study GRACE (44695 patients), conducted in different countries of America and Europe, shorter intervals of pre-hospital delay were reported in groups of patients with STEMI and non-STEMI [15]. The mean pre-hospi-

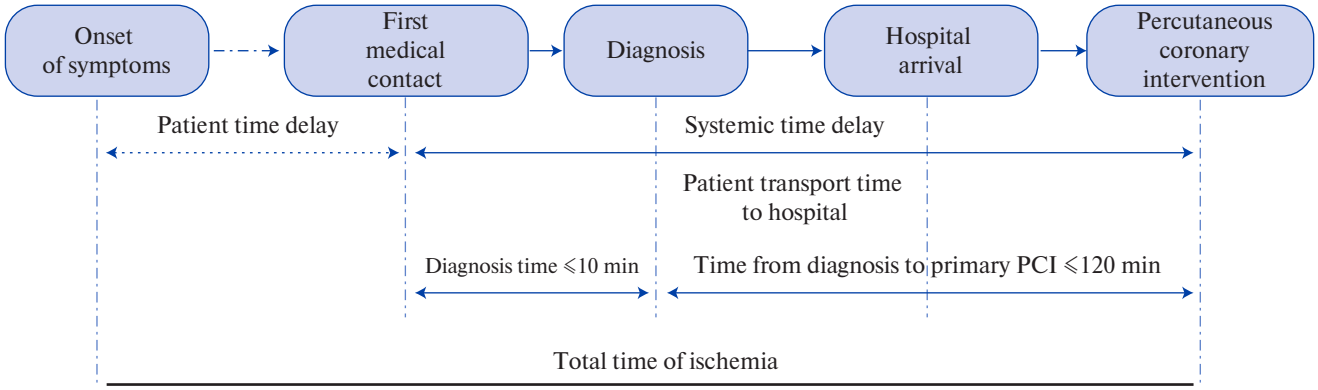


**Fig. 1.** Components of delayed medical care for MI.

tal delay was the shortest (2,5 hours) in patients with STEMI, while in patients with non-STEMI/unstable angina, there was a longer pre-hospital delay (3,1 hours).

At the same time, in some studies, there was a tendency to a slight decrease in the average time from the onset of the symptoms to the hospital arrival. For example, a comparison of the first and second parts of the EHS-ACS program in terms of time delay showed a decrease in the average time from the onset of ACS symptoms to arrival at the emergency room from 210 min (105-625) in EHS-ACS-I (2000) to 170 min (90-420) in EHS-ACS-II (2004) [16]. This reduction was the result of a decrease in both the time from the onset of disease symptoms to sought treatment, an average of 120 minutes (50-450) in EHS-ACS-I to 105 minutes (40-306) in EHS-ACS-II, and time from the first medical contact (FMC) to arrival at the emergency room, on average from 50 minutes (26-91) in EHS-ACS-I to 42 minutes (15-80) in EHS-ACS-II. At the same time, it was noted that the reduction in time over the indicated period was apparently associated with information campaigns for target population about the need for an immediate response in case of ACS symptoms.

According to European data, the time interval from a call to an emergency MC (EMC) to the FMC should not exceed 20 minutes, and in the Russian EMC this target should also fall within a 20-minute interval [17]. It should be noted that in the organizational plan, further target reduction is no longer possible. In this regard, it is necessary to redirect efforts to optimize the initial time interval from the moment of development of the first ACS symptoms to the sought treatment. According to American standards for EMC for patients with STEMI, the maximum time interval for percutaneous coronary intervention (PCI) should be no more than 120 minutes, while the recommended target time from beginning of symptoms to call to EMC is no more than 5 minutes [18].

So, in the American randomized study IMMEDIATE (871 patients), conducted from 2006 to 2011, the average time from the onset of ACS symptoms to call to EMC was 53 minutes. It is less than in previous studies (NRMI-2, GRACE), but much longer than the target time recommended by the American College of Cardiology [19].

In the prospective observational study ACCESS (11731 patients), conducted in developing countries in Africa, Latin America and the Middle East, the median delay time in the pre-hospital stage was significantly longer and amounted to 4 and 6 hours for patients with STEMI and non-STEMI ($p<0,0001$), respectively [20]. According to the Indian CREATE registry (20937 patients), the median time from symptom onset to hospitalization in patients with STEMI was 5 hours [21].

According to large multicenter observational studies (CREATE, ACCESS, etc.) conducted in developing countries, a greater number of cases of STEMI, longer intervals of pre-hospital delay were recorded. It was largely explained by differences in the level of education, social status and differences in EMC organizing system in developed and developing countries [20, 21].

**Delays in seeking for MC according to Russian studies**

The results of domestic registers [5, 22–25] which have timeliness analyses of providing MC to patients with ACS/MI at the pre-hospital stage, are generally comparable with the data of foreign studies [15, 16].

Meanwhile, in the study performed in the period from 2004 to 2007 on the basis of several Moscow

clinics, it was found that in most cases, patients with MI seek for MC no earlier than 7 hours after the onset of the first symptoms, moreover, after more than 12 h — 45-53% of patients [23].

In a single-center domestic LIS register with 363 MI patients included from 2010 to 2011, half of the patients took less than 40 minutes to make an decision to call an EMC. However, almost a third of patients applied for MC after an hour or more from onset of the pain syndrome that caused hospitalization with ACS [24].

Quite interesting was the analysis of pre-hospital stage delays according to a series of Russian registers of acute coronary syndrome RECORD. So, the time from the onset of symptoms to hospitalization in a "non-invasive" hospital according to the RECORD-2 register (2009-2011) compared with the results of RECORD-1 (2007-2008) was shorter as in STEACS (3,2 versus 4,1 h, p=0,03), and non-STEACS (4,0 versus 6,5 h, p<0,0001) [25]. According to the "new" RECORD-3 register (2015), which includes much more patients (2370 people), the median time from the onset of symptoms to the first sought treatment was 3,4 hours (1,0-16,8), from FMC to admission to hospital — 1,5 hours (1,0-3,1) for both types of ACS [22].

When comparing data of Monitoring and Register of ACS for 2016, the average time from beginning of symptoms to call to EMC was 115 (60; 177) minutes. According to the data of the ACS Register for the same period, this parameter was 130 (40; 450) minutes. Time medians were comparable and no significant differences between it were found (p>0,05) [5].

As part of the implementation of the national program for the care of patients with acute CVD in the Russian Federation, one of the significant achievements, along with an increase in the quality of specialized care and the number of PCI procedures, is the reduction of all possible time delays from the onset of MI symptoms to reperfusion therapy. But it is mainly due to systemic factors [7]. For example, on the basis of the Kemerovo Regional Vascular Center in 2014 the following time data were achieved: time from beginning of symptoms to call to EMC was 135 minutes, from call to FMC was 27 minutes, and the time period from FMC to PCI was 54 minutes. It is less than the time intervals for 2008 (142, 32 and 40 min, respectively) [26].

Thus, the results of most studies conducted in both developed and developing countries indicate that the majority of the delay in patients with ACS occurs from the moment of first symptoms to patient decides to call to EMC, which is approximately 2/3 of the entire pre-hospital stage [27]. Therefore, one of the priorities in the fight against cardiovascular mortality is a further analysis with a focus on the pre-hospital stage of ACS/MI treatment.

**Factors associated with delayed call to EMC**

Currently, there are a sufficient number of studies of factors that influence the decision of a MI patient to call to MC. Unfortunately, the results of these studies cannot always clearly determine which of the factors, or their combination, determines the timeliness of a patient's decision to call to MC.

It is known that such socio-demographic characteristics as female gender, old age, and low educational level increase the time until MI patient arrives in the intensive care unit, which was confirmed in review studies [28]. An epidemiological study revealed a negative trend, reflecting an increase in mortality from MI in females [29]. This was largely explained by the peculiarities of clinical manifestations — the predominance of atypical variants of MI in women, which served as an explanation for later treatment among this category. At the same time, according to Efremova O. A. et al. (2015), risk of atypical MI variant remains significantly higher in males aged 56-70 years [30]. In turn, the results of large observational studies also do not confirm the presence of gender differences in the development of atypical MI variants [31].

It should be noted that recently there were publications that cast doubt on the independent contribution of the female sex as a separate factor associated with an increase in the time delay at the pre-hospital stage in patients with MI [31, 32]. So, according to the results of a German study, there was no direct relationship between the female gender and the delay in deciding to call an EMC [31]. According to another study [32], it was also shown that younger women had shorter delay times at the pre-hospital stage compared to men. In the above studies, the authors draw attention to the fact that a combination of two factors (women and the elderly (over 65 years)), is possible to have a synergistic effect, which forms the target group [31, 32]. Similar results were reported in the NRMI register, which included more than 482 thousand patients with STEMI [33]. The study found that in a subgroup of patients with a combination of several factors (old age (70 years and older), female gender, Negroid race or Hispanics, diabetes mellitus), the delay time before arrival to the hospital was significantly longer compared to the reference group (without combination of these characteristics).

Patients with STEMI arrive at the hospital much faster than patients with non-STEMI [12, 20]. Obviously, time difference in admission to the hospital can be explained in terms of the ACS pathogenesis, which determines the development of the corresponding clinical picture of MI. In particular, Perkins-Porras L, et al. (2009) suggest that patients diagnosed with STEMI have symptoms that are likely to be considered more severe, which may increase their motivation for more rapid call to EMC [27].

The development of MI, accompanied by the manifestation of nonspecific symptoms (eg, dyspnea, nausea, weakness), was associated with a long delay of the patient at the pre-hospital stage [34].

In other studies, a clear connection was found between a correct interpretation of the symptoms of MI and a reduction in the time of pre-hospital delay [27]. O'Donnell S, et al. (2014) report that in 65% of patients, the development of ACS was accompanied by a slow onset and moderate pain, while 35% of patients had a classic onset of ACS with the development of an intense pain [11], which makes it difficult to interpret the symptoms of MI as for the patient and for the medical workers.

As for such a characteristic as marital status, ambiguous data are provided in various sources. So, in a prospective study by Fathi M, et al. (2015), it was shown that married patients postpone a visit to a doctor for a longer period, and, on the contrary, patients living alone more quickly apply for MC [35]. The results of the study by Perkins-Porras L, et al. (2009) are consistent with data from Moser D, et al. (2006), which show that marriage and the presence of observer (friend, colleague) were associated with a shorter time for deciding to apply for MC [27, 36]. In contrast, according to studies by Raczynski JM, et al. (1999) and Bolivar J, et al. (2013), family members (especially spouses) increase the delay time before calling the ambulance, trying to propose alternative strategies, while the presence of observer tended to reduce the time of arrival to the intensive care unit [35].

Among the psychoemotional factors associated with the delay of a patient with ACS before hospitalization, a number of authors distinguish anosognosia (denial of their disease) and depressive disorder [37]. So, for example, in a study by Bunde J and Martin R (2006), which included 433 patients, the revealed depressive state, as well as weakness, sleep disturbance and exhaustion, were correlated with a longer patient's decision to apply for MC [38].

According to the Russian LIS register, the rather frequent reasons for late sought treatment of patients with ACS were the fear of hospitalization, the reluctance to disturb the medical workers, and the erroneous assumption that the symptoms may go away on their own or do not pose a serious danger [24].

The level of medical literacy is important in the decision to apply for MC, which was discussed in some works [23, 39]. It was reported that often patients cannot recognize symptoms of ACS in time, attributing them to other diseases [40], due to insufficiency of information on algorithms for providing MC and alertness for the main symptoms of the disease [23].

In a study by Farshidi H, et al. (2013) it was shown that a high level of education and a burdened family history of CVD reliably correlate with a reduction in the time of arrival at the hospital from the onset of MI symptoms [41]. The researchers obtained data that in 73,1% of patients, ignorance of the main CVD risk factors and underestimation of disease severity are causes of untimely sought treatment for MC, and were reliably associated with a low level of education and a lack of CVD history. As noted by Thuresson M, et al. (2007) in their study, 3/4 of the patients were able to correctly interpret the symptoms of MI, as they were previously aware of this disease [39].

The MC time delays in ACS patients at the prehospital stage are also determined by population density, area (urban, rural) [42], geographical features [43], etc.

In the studies of domestic researchers, systemic time delays in rural areas are mainly due to a possible difference in the educational status of urban and rural residents, the low availability of MC in the village, and lack of transport links [42].

Separately, it is also worth dwelling on the geographical features of Russia. It is the main reason for the patient's delay on the way to the PCI center, due to its rather large extent, the significant remoteness of settlements from medical organizations and limited transport links in several regions of the Russian Federation [43].

**Interventions aimed at improving the literacy of the population and reducing the time for sought treatment**

According to experts, a reduction in cardiovascular morbidity and mortality in the Russian Federation can only be achieved if comprehensive measures are taken to prevent and control CVD complications and to increase the level of public awareness of symptoms and the course of action in ACS/MI [1].

Dracup K, et al. (2009) reported that through educational programs among patients with high cardiovascular risk, an increase in the frequency of aspi-

rin use by patients with ACS at the pre-hospital stage was noted [44]. In an earlier American study by Wright R, et al. (2001) it was shown that the implementation of an educational project to increase public awareness of MI symptoms contributed to a significant increase in the number of calls to EMC [45].

An analysis of domestic and foreign literature sources [23, 39, 41], as well as the results of large-scale sociological surveys conducted in our country, showed extremely low awareness of the population about CVD risk factors, MI signs and symptoms, as well as measures to prevent it. All of the above mean the need for a large-scale educational campaign to increase public awareness of the main IM symptoms, the importance of fast call to EMC, as well as increasing adherence to a healthy lifestyle among the population.

An example of such campaigns is the social project "Act Fast! Save life!", implemented in the Samara region as part of the European Stent for Life initiative [7]. Also there are a number of social and educational programs "Pulse of Life", "Health Index of the Future", implemented in Russia by joint efforts of medical workers, media, involving administrative and other resources. Various events are considered as the main project tool (including on-site seminars, outdoorsy events, conferences, TV shows), aimed primarily at reducing cardiovascular mortality by increasing awareness of the importance of early sought treatment for MC in case of ACS symptoms.

In our opinion, the results of the Swedish study (820 patients) are interesting. In this research authors study characteristics of the MI symptoms and changes of the time interval from the onset of the symptoms to FMC in the primary and repeated MI in the same patient [46]. It was noteworthy that a small number of patients (10% of men and 16,2% of women) reported a different characteristics of symptoms in primary and repeated MI. Moreover, patients with a pre-hospital delay of $\geqslant$2 h with primary MI were more likely to have similar temporary indicators of pre-hospital delay with repeated MI. Researchers concluded that according to the patient's behavior during primary MI, they can predict how they will lead yourself with repeated MI. Therefore, in the development of preventive action algorithms in ACS, a personalized approach is necessary, taking into account certain prognostic factors (for example, old age, concomitant diseases, etc.) and sociological characteristics [38].

One of the extremely important aspects that deserves special attention is the oligosymptomatic and asymptomatic MI course. In a study by O'Donnell S, et al. (2014) it was noted that with the development of atypical MI variants, most patients have difficulties in interpreting their clinical status, which leads to an increase in the time from the onset of symptoms to treatment for MC [11]. Given the above data, it is necessary to consider the need to include information on certain variants of MI to educational events.

## Conclusion

The delay in applying for MC for patients with ACS/MI is currently a significant factor in determining the effectiveness of the treatment of these diseases. Over the past decades, modern methods of treatment, clear recommendations from the health system have been developed. Meaningful progress has been made in reducing the time from calling the EMC to receiving treatment, especially in developed countries.

With regard to the behavior of patients, that is, the time from the onset of symptoms to treatment for MC progress is significantly less. Many patients require more than two hours to make a decision about calling an ambulance, which significantly reduces the probability of effective treatment. A number of modified and non-modified factors associated with the decision making speed of patients are demonstrated. A significant factor is the medical literacy of the population, that is, awareness of the symptoms and the ability to recognize them and seek help in time.

In the world and in Russia, experience in conducting interventions at the population level has been accumulated. It aimed at improving the literacy of the population in terms of symptoms of MI/ACS and the importance of timely treatment for MC.

Today, there is no doubt that, along with organizational measures aimed at fight against CVD (improving the MC quality, increasing the coverage of dispensary care, optimizing the system of ambulance care), enhancement the awareness of the population about the ACS symptoms and the course of urgent action should be considered as one of priority areas.

**Conflicts of interest:** nothing to declare.

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# Association of stress with cardiovascular diseases and risk factors in a population (ESSE-RF in Kemerovo region)

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**Aim.** To assess the prevalence of stress and its association with socio-demographic characteristics, cardiovascular risk factors and cardiovascular diseases (CVD) in the Siberian population.

**Material and methods.** A cross-sectional study was performed in the framework of the Russian multicenter epidemiological study ESSE-RF in the Kemerovo Region in 2013. The presented study included 1628 individuals aged 25 to 64 years. Information was assessed on the presence of stress, some socio-demographic and economic characteristics, a history of CVD, as well as behavioral habits and quality of life. To eliminate the modifying effect of socio-demographic characteristics, a logistic regression analysis was used. The odds ratio (OR) and the 95% confidence interval (CI) were calculated.

**Results.** The prevalence of stress was 22,6%; stress was statistically significantly more often recorded in women (28,1%) than in men (11,7%). After adjusting for socio-demographic characteristics, stress was statistically significantly more often recorded in people with secondary and primary education compared with those with higher education (24,9% and 19,1%, p=0,006), as well as in people with middle and high financial affluence compared with low affluence (24,5% and 11,3%, p<0,001). This association is observed only at the expense of women. For unemployed participants, the stress rate is higher only among males — 18,8% versus 11,4% among workers (p=0,015). Stress was also statistically significantly more often recorded in groups with arterial hypertension, lack of sleep, quality of life on the EQ-VAS scale and on the EuroQol scale. Smokers are more likely to have stress (23,8% vs 22,0%) and have a history of stroke (35,3% vs 22,2%). Among all CVDs and their risk factors, an inverse association of stress with obesity was revealed only in men.

**Conclusion.** Study showed that people with stress are under large load of some cardiovascular risk factors. At the same time, ambiguous associations between stress and arterial hypertension and quality of life were obtained. This confirms the need for further study of the association of stress with other factors of cardiovascular risk, taking into account age and gender and socio-economic characteristics of the population.

**Key words:** stress, risk factors for cardiovascular diseases, epidemiological study.

**Conflicts of Interest:** nothing to declare.

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It is known that stress can act as a trigger for the development of cardiovascular disease, initiating a systemic inflammation, which may lead to adverse consequences especially for people with low socio-economic status [1]. However, the contribution of stress to the cause-effect relationships with socio-demographic, behavioral, and psychological risk factors for cardiovascular disease (CVD) is still a subject of discussion. That is because there is no definitive answer to the question of which mechanisms of initiation play the main role in triggering of complex stress-induced pathophysiological processes. The assessment of such a risk factor as stress may include several components and seems to be a laborious and complex process. The reason for this is the lack of a unified assessment of stress, which to some extent may affect the obtained associations [2, 3]. In addition, stress-induced complex body reactions can lead to the development of CVDs in the delayed observation period. INTERHEART study of a representative sample of 24767 people from 52 countries showed that stress doubles the risk of acute myocardial infarction, and this association did not depend on the region of residence, ethnicity, and gender [2]. Another prospective study of the effects of cumulative stress on cardiovascular risk shows association with age, ethnicity, marital status, as well as smoking and obesity, diabetes, depression, and anxiety [4]. As past studies have shown, it is important to take into account the interpretation of the events that have taken place when studying stress, as the same events can have a diametrically opposed meaning for different individuals. Despite differences in research methods (in samples differing in sex, age, and ethnic composition), the negative contribution of stress to the pathogenesis of CVDs has been undisputed for several decades [5]. Difficulties in studying the interaction of stress with cardiovascular risk (CVR) factors and CVDs have led to the accumulation of a vast array of epidemiological, clinical, experimental and pathophysiological studies. However, there are still unresolved issues in the literature regarding the cause-effect relationships between stress and CVDs. It is known that these associations are influenced by external factors (climatic and geographical conditions, legislative and social environment of the region), internal features of the organism (presence of comorbid pathology, certain socio-demographic and behavioral factors, individual susceptibility to stress). Taking into account that the life of any modern person is inseparably associated with stress, its study is given an important place as one of the modifiable CVR factors.

The aim of the study was to assess the prevalence of stress and its associations with socio-demographic characteristics, CVR factors and CVDs in the Siberian population.

## Material and methods

The study was carried out as part of the Russian multicenter epidemiological ESSE-RF study in the Kemerovo region in 2013. It included 1628 surveyed persons aged 25 to 64 years.

The questionnaire survey provided information on socio-demographic characteristics (sex, age, education, marital status, employment), stress, behavioral habits (alcohol, smoking, lack of sleep and low physical activity), history of CVD (arterial hypertension, coronary artery disease (CAD), cerebrovascular accident, diabetes mellitus), economic conditions (financial wealth), quality of life.

The criterion of arterial hypertension was considered to be the level of blood pressure $\geqslant$140/90 mm Hg, or lower against the background of hypotensive therapy. CAD presence was assessed on the basis of three epidemiological criteria: coding of electrocardiographic changes according to Minnesota code, Rose questionnaire and history of myocardial infarction.

Obesity was defined as value of body mass index >29 kg/m$^2$. Hypercholesterolemia was diagnosed with total cholesterol levels >5,0 mmol/l, as well as taking of lipid-lowering drugs (mainly statins) in the history. Fasting hyperglycemia was diagnosed with plasma glucose level of venous blood >5,6 mmol/l.

Alcohol consumption was estimated based on the frequency, volume and type of drink consumed. The volume of alcohol consumed per year was calculated and converted to average daily values in grams of ethanol. Those who consumed more than 24 grams of ethanol per day were considered as alcohol abusers.

Smokers were those who smoked at least one cigarette a day or quit smoking less than 1 year ago.

The Perceived Stress Scale was used to determine susceptibility to stress. This scale consists of 10 questions that determined how stressful the previous month was [6]. The order of series obtained was used to calculate the 75th percentile, the values above were considered as a risk factor (5 points and above).

Insufficient sleep was considered to be night's sleep at duration of <7 hours. Insufficient physical activity was taken in case of activity <5 times per week for 30 min (moderate) or physical activity <3 times per week for 20 min (intensive). The level of physical activity was considered to be low

if it was below the minimum recommended level of 150 minutes of moderate or 75 minutes of intensive aerobic exercise per week for adults (medium or high speed walking, or equivalent exercise).

The EUROQOL-EQ-5D international questionnaire and EQ-VAS visual analogue scale were used to assess the quality of life. It was used to score 5 components of the quality of life (mobility, self-care, usual activity, pain/discomfort, anxiety/depression). Each component was assigned 0 points for the absence of disorders, 1 point for moderate disorders and 2 points for severe disorders. The sum of the scores was used as a quantitative assessment of the quality of life. According to the visual analogue scale, interviewers assessed their health status in scores from 0 to 100.

The study was conducted in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Research Institute for Complex Issues of Cardiovascular Diseases. Prior to inclusion in the study, written informed consent was obtained from all participants.

The analysis of stress prevalence depending on socio-demographic characteristics of the sample, presence of cardiovascular diseases and CVR factors was carried out using the Pearson's Chi-square test. Differences in quantitative parameters (age, quality of life according to EQ-VAS and EUROQOL scales) in persons with/without stress were assessed using the Mann-Whitney test and were represented by mean values and standard deviation.

Significant differences in stress prevalence depending on socio-demographic characteristics may affect the association of stress with CVDs and SSR factors. Logistic regression analysis was used to eliminate the modifying effect of socio-demographic characteristics. At the same time, the associations studied were adjusted for the impact of gender, age, employment, level of education, marital status, urban/rural residence, and financial well-being. The odds ratio (OR) and 95% confidence interval (CI) were calculated.

A critical level of statistical significance was 0,05.

## Results

**Association of stress prevalence with socio-demographic characteristics.** The prevalence of stress was 22,6%, and in women (28,1%) it was statistically significantly higher than in men (11,7%), respectively (OR=0,37, 95% CI=0,28-0,49).

Stress prevalence and its association with socio-demographic characteristics are presented in Table 1. Univariate analysis shows differences in stress prevalence depending on gender, employment, level of education, marital status and financial well-being. Thus, stress is statistically significantly more often registered in the unemployed, compared to those who have job (27,2% and 21,0%, p=0,009), persons with secondary and primary education, compared to those with higher education (24,9% and 19,1%, p=0,006), individuals without a family, compared to those with a family (26,5% and 19,8%, p<0,001), participants with medium and high income, compared to those with low income (24,5% and 11,3%, p<0,001).

After adjustment for socio-demographic characteristics, the association with stress became statistically insignificant for such parameters as employment and marital status. In other cases, the regularities remained the same.

**Association of CVR factors with stress in different gender groups.** An analysis of CVR factors and stress relationships in men and women revealed an association between stress and secondary and primary education, as well as financial well-being (only for women). Thus, stress is more often recorded in women with secondary and primary education (33,4%) compared with higher education (24,2% (p=0,002)), and less often in women with low incomes — 13,5% versus 32,2% (p=0,001). For unemployed, the stress prevalence is higher only among males — 18,8% versus 11,4% (p=0,015). The adjustment for socio-demographic characteristics did not change the above associations.

**Association of stress with CVDs and CVR factors.** Univariate analysis showed differences in associations between stress prevalence and arterial hypertension, CAD, as well as factors such as sleep adequacy, alcohol abuse, and average quality of life (both EQ-VAS and EUROQOL) (Table 2). The stress frequency is lower in persons with arterial hypertension than without it (19,7% and 24,8%, p=0,012, respectively), as well as in alcohol abusers, compared to those who do not abuse alcohol (18,9% and 25,6%, p<0,001). In contrast, the stress rate was higher in the group with lack of sleep (29,0% vs. 20,0%, p<0,001) and CAD (30,7% vs. 20,9%, p<0,001). The quality of life of persons with recorded stress, as compared to those without it, was higher on both the EQ-VAS scale (67,9±16,1 vs. 59,6±16,8, p<0,001) and the EUROQOL scale (1,36±1,34 vs. 2,52±1,53, p<0,001).

Adjustment for socio-demographic characteristics has not changed the importance of associations with

**Table 1**

**Associations of stress with socio-demographic characteristics**

| Characteristics | | N | Stress | | Logistic regression | | |
|---|---|---|---|---|---|---|---|
| | | | %, M±SD | P | OR | 95% CI | P |
| Sex | Males | 700 | 11,7 | <0,001 | 0,37 | 0,28-0,49 | <0,001 |
| | Females | 928 | 28,1 | | | | |
| Age | Stress | 367 | 45,6±11,4 | 0,10 | 1,00 | 0,99-1,01 | 0,86 |
| | No stress | 1258 | 47,6±11,2 | | | | |
| Age groups (years) | 25-34 | 331 | 21,2 | 0,20 | – | – | – |
| | 35-44 | 332 | 19,1 | | | | |
| | 45-54 | 434 | 25,1 | | | | |
| | 55-64 | 531 | 23,6 | | | | |
| Employment | Yes | 255 | 21,0 | 0,009 | 0,84 | 0,63-1,11 | 0,22 |
| | No | 112 | 27,2 | | | | |
| Secondary education | Yes | 245 | 24,9 | 0,006 | 1,37 | 1,05-1,78 | 0,019 |
| | No | 122 | 19,1 | | | | |
| Lack of family | Yes | 172 | 26,5 | <0,001 | 1,08 | 0,84-1,39 | 0,56 |
| | No | 191 | 19,8 | | | | |
| Rural residence | Yes | 66 | 23,9 | 0,6 | 0,96 | 0,69-1,32 | 0,79 |
| | No | 300 | 22,5 | | | | |
| Low income | Yes | 27 | 11,3 | <0,001 | 0,42 | 0,27-0,65 | <0,001 |
| | No | 340 | 24,5 | | | | |

stress in the groups: with arterial hypertension (OR=0,75, 95% CI 0,57-0,98), lack of sleep (OR=1,72, 95% CI 1,33-2,22), quality of life on the EQ-VAS scale (OR=0,07, 95% CI 0,96-0,98) and on the EUROQOL scale (OR=1,66, 95% CI 1,51-1,82). Associations of stress with alcohol abuse and CAD were not statistically significant. On the contrary, there were statistically significant associations of stress with smoking and stroke in the history: stress was observed more likely in smokers (OR=1,61, 95% CI 1,21-2,14) and persons with stroke in the history (OR=2,21, 95% CI 1,04-4,73).

**Association of stress with CVDs and CVR factors in different sexual groups.** Among all CVDs and their CVR factors, only males have an inverse relationship between stress prevalence and obesity. Thus, association of stress prevalence with obesity in men was statistically significantly lower (8,7% vs. 14,7%, respectively, p=0,03), After adjustment for socio-demographic characteristics the significance of the association has not changed (OR=0,54, 95% CI 0,30-0,95). No other associations between stress and CVDs depending of sex were found.

## Discussion

Thus, according to the survey results, the prevalence of stress was 22,6%. In women, stress was statistically significantly recorded almost 2 times more often than in men. The high prevalence of stress in women was also observed in the Swedish national study [7], which may indicate a strong association between stress and female sex.

Sleep disorders, like stress, are an important problem in modern society.

A number of studies have found that sleep disorder increases the risk of various diseases, including CVDs. A nationwide Japanese study of the relationship between sleep disorders and stress showed that people who felt high levels of stress were more prone to sleep disorder [8]. In study of Alosaimi FD, et al. (2015) a similar positive association of stress with lack of sleep was observed [9]. Our study obtained a statistically significant direct relationship between insufficient sleep and stress. Behavioural habits such as drinking and smoking were also positively related to sleep disorders. Smoking, as a strategy for correction of sleep disorder, is known to contribute significantly to sleep pathologies. Smokers are more likely to experience sleep disorders such as night apnea, defect sleep quality, insomnia, which, in turn, are risk factors for the development of many chronic diseases of modern civilization (obesity, CVDs, diabetes) [10].

In this study, a statistically significant association of bad habits (smoking and alcohol abuse) with stress

**Table 2**

**Associations of stress with CVR and CVD factors**

| Risk factors | | N | Stress | | Logistic regression | | |
|---|---|---|---|---|---|---|---|
| | | | %, M±SD | P | OR | 95% CI | P |
| Lack of sleep | Yes | 135 | 29,0 | <0,001 | 1,72 | 1,33-2,22 | <0,001 |
| | No | 232 | 20,0 | | | | |
| Low physical activity | Yes | 92 | 22,3 | 0,9 | 1,16 | 0,86-1,56 | 0,91 |
| | No | 265 | 22,4 | | | | |
| Smoking | Yes | 118 | 23,8 | 0,42 | 1,61 | 1,21-2,14 | <0,001 |
| | No | 249 | 22,0 | | | | |
| Alcohol | Yes | 139 | 18,9 | <0,001 | 0,99 | 0,75-1,30 | 0,92 |
| | No | 228 | 25,6 | | | | |
| Quality of LIfe (EQ-VAS) | Stress | 367 | 67,9±16,1 | <0,001 | 0,97 | 0,96-0,98 | <0,001 |
| | No stress | 1258 | 59,6±16,8 | | | | |
| Quality of life (EUROQOL) | Stress | 367 | 1,36±1,34 | <0,001 | 1,66 | 1,51-1,82 | <0,001 |
| | No stress | 1258 | 2,52±1,53 | | | | |
| Hypercholesterolemia | Yes | 194 | 22,6 | 0,97 | 0,91 | 0,71-1,18 | 0,48 |
| | No | 171 | 22,7 | | | | |
| Hyperglycemia | Yes | 59 | 21,2 | 0,53 | 0,88 | 0,63-1,24 | 0,47 |
| | No | 306 | 22,9 | | | | |
| Arterial hypertension | Yes | 139 | 19,7 | 0,012 | 0,75 | 0,57-0,98 | 0,032 |
| | No | 228 | 24,8 | | | | |
| Coronary artery disease | Yes | 83 | 30,7 | <0,001 | 0,99 | 0,98-1,01 | 0,12 |
| | No | 280 | 20,9 | | | | |
| Stroke | Yes | 12 | 35,3 | 0,074 | 2,21 | 1,04-4,73 | 0,040 |
| | No | 351 | 22,2 | | | | |
| Obesity | Yes | 124 | 21,7 | 0,53 | 0,80 | 0,61-1,04 | 0,099 |
| | No | 242 | 23,1 | | | | |
| Diabetes mellitus | Yes | 13 | 20,6 | 0,71 | 0,92 | 0,48-1,76 | 0,80 |
| | No | 350 | 22,6 | | | | |

has been identified among both smokers and alcohol abusers. However, after adjustment for socio-demographic factors, the significance of the stress relationship remained only for smokers.

Stress has long been recognized as a risk factor for smoking. There is ample evidence, both epide-miological and clinical, of the direct association between stress and substance use behaviour. Stress also relates to both smoking addiction and its successful cessation. For example, past studies have shown that smokers have a higher level of stress than non-smokers and former smokers [11].

It is known that the quality of life directly depends on socio-demographic, anthropometric, anamnestic, psychological factors, as well as the current morbid status. However, there is still no consensus on the factors influencing the quality of life. At the same time, certain nosologies are characterized by their own set of the most studied factors influencing the quality of life. In this study, the reverse association of stress with quality of life is obtained both on the EUROQOL-EQ-5D scale and on the EQ-VAS scale. In this study, people with stress have a higher quality of life than those without it. Thus, stress has been associated with higher quality of life values, which indicates a complex relationship between quality of life and stress.

The study found an association of stress with obesity only in men. Obesity was statistically significantly less common in men with stress than in men without stress. According to the literature, the evidence of the relationship between stress and body mass index is rather contradictory. On the one hand, given the relationship between stress and the addictions underlying many chronic diseases, stress contributes to weight gain, including obesity [10]. On the other

hand, a meta-analysis of data from 1,617,46 participants in 13 European studies (49% of men, mean age 43,7 years) showed that stress associated with hard work can be associated with both weight gain and loss, reflecting a U-shaped association of stress and body mass index [12]. In the study by Boyce JA, et al. (2014) examining stress and body mass index in New Zealand freshmen showed that students with high levels of stress gained weight if they had an initial high body mass index, and lost weight in case of initial low body mass index [13].

Previous studies have proven the role of chronic stress in the formation and progression of arterial hypertension in particular and CVDs in general, directly potentiating systemic inflammation, as well as indirectly influencing behavioral changes. In a study by Lu X, et al. (2019) shows that the association of stress with arterial hypertension changed by gender and ethnicity [14]. Asian-American men with high levels of stress were significantly more likely to develop arterial hypertension than men with low stress. There was no association between perceived stress and hypertension for females. In our study of the relationship between stress and arterial hypertension, no association was found for both men and women. On the contrary, persons with normal blood pressure were more likely to experience stress than persons with hypertension. After adjustment for socio-demographic factors, the statistically significant relationship between hypertension and stress did not change.

Work and stress are inseparably associated in modern society, affecting each other. The results of the research show that people with jobs were less stressed than unemployed people. The unemployed had a higher prevalence of stress only because of their male counterparts, which suggests that stress was more related to unemployment among men than women. This is confirmed by the literature, where a cohort study by Mæhlisen MH, et al. (2018) found that domestic stress almost doubled the risk of unemployment [15].

It is known that chronic stress increases the risk of CAD [1, 2]. INTERHEART's study in a representative sample of 52 countries showed that stress doubles the risk of myocardial infarction, regardless of gender, race, or region of residence. In this study, people with CAD were more likely to have stress than people without CAD, but this association was not strong in case of elimination the modifying effects of socio-demographic characteristics. Thus, we did not get a significant association of stress with CAD. The REGARDS's study showed that groups of people with high levels of stress were at increased risk of CAD, but only for those with below average income [16].

Poverty is known to be a source of chronic stress and can have a negative impact on both physical and mental health. At the same time, it can be ambiguously perceived by the population, as indicated by study of Hjelm L, et al. (2018) examining the impact of state poverty alleviation programmes on stress among poor households in Zambia, South Africa. The study found that financial programmes did not change the frequency of stress, but that this improved food security associated with improved food quality, resulting in an indirect reduction in the prevalence of stress [17]. Absence of associations of financial income with stress was also noted in another study [9]. However, persons over 60 years old have an association between low income and higher levels of stress [7], which indicates a modifying effect of age. In the present study, stress was almost twice as rare in low-income individuals as in middle- and high-income individuals. Adjustment for socio-demographic factors did not change the importance of association. However, this association was observed only at the expense of women.

A statistically significant association of secondary education and stress is obtained. Thus, among individuals with secondary education stress prevalence is higher than with higher education. Moreover, this association is observed among women. Thus, women with secondary education were statistically significantly more likely have stress. For men, the association of the level of education with stress was not found in our study. In the study by Hjelm L, et al. (2018) among poor households in Zambia, the level of education also did not show a strong association with stress among both men and women [17].

However, in a population study examining the prevalence of stress after 65 years of age, higher average levels of d stress were associated with low levels of education [7].

Stress was less common among married people than among single people, but the adjustment for socio-demographic factors led to a leveling of this relationship. The absence of a relationship between marital status and stress was also noted in the study by Alosaimi FD, et al. (2015) [9]. At the same time, in a population study, singlehood was statistically significantly associated with stress in older persons [7].

## Conclusion

Thus, when studying the relationship of stress with CVD risk factors, it was revealed that stress is

more often recorded in women and in people with lack of sleep. Socio-demographic factors such as secondary education and financial well-being are also closely related to stress.

It has been shown that people with stress have a large load of some CVR factors. At the same time, ambiguous associations of stress with arterial hypertension and quality of life were obtained.

It is noteworthy that these associations remained after the adjustment for the socio-demographic factors. This confirms the need for further study of the association of stress with other CVR factors, taking into account the sex, age and socio-economic characteristics of the population, to identify the effects of stress on the cardiovascular system.

**Limitations.** An important limitation due to the cross-sectional design of the study is the inability to draw conclusions about the cause-effect associations. We have also not studied the contribution of depression, which in itself can cause stress and, conversely, lead to additive effect. We have not studied the modifying effects of age and socioeconomic status, although there is evidence that age may influence the associations obtained, and low socioeconomic status is an aggravating factor for stress. In addition, stress levels were not graded, which could lead to ambiguous interpretation of the results.

**Conflicts of Interest:** nothing to declare.

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# Humanitarian competencies of a doctor (cardiologist)

Taratukhin E. O.

The article reveals the features of working with the patient as a social and psychological subject, who, in addition to somatic pathology, has an experience of the disease situation. Psychosocial risk factors for cardiovascular (and more generally non-infectious) pathology, as well as social well-being as a component of positive health, are considered as elements of a doctor-patient relationship. Work with a person requires from a doctor competency that differs from working with pathology at a biological level. Perhaps, the time has come to single out "biomedical doctors" and "medical doctors" in clinical medicine, of which the first ones are not required humanitarian competencies. Since non-infectious pathology largely includes psychosomatic features, and mental processes are filled with an experience of social reality, the clinician must have skills of human sciences to work with them. This is especially important in view of the physician's power as an ambassador of medicine and health. The following competencies are discussed: internal work skills, situational search and interpretation, communicative and ethical competence, development of positive health.

**Key words:** psychosocial risk factors, health, psychosomatics, non-communicable diseases, patient orientation, psychocardiology, medical ethics, continuing education.

**Conflicts of Interest:** nothing to declare.

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Higher education standards include the concept of general professional and universal competencies. This level of competence combines the knowledge and skills typical of a person with higher education in general and a doctor as a specialist in particular.

Among the universal competences (in the project of Federal State Educational Standard of Higher Education with account of professional standards in the specialty 31.05.01 — Medical Doctor [1]), as well as among general cultural, general professional and professional (in the current FSES HE 31.05.01 — Doctor — medical care [2]) should be highlighted a number of related to humanitarian knowledge (Table 1).

In addition, in the case of primary specialized accreditation in cardiology, the "Communication" station of the objective structured clinical examination includes situations of "difficult" patient" and "bad news" [3].

The doctor is a representative of medicine. Medicine — teaching, private science, practice, cultural phenomenon that has formed in the millennia of confrontation with nature. Its task is to prolong life with maximum quality, to preserve and achieve full health — well-being on the physical, mental and social levels of human being [4].

Man is biosocial in nature. Bioelectricity creates conditions for thinking and communication, which are realized in the form of symbols expressed, perceived and interpreted by people. This is how culture is created — the second nature or everything that is not nature.

Work in medicine requires taking into account 1) the biological side of man, his physiology and pathology, 2) the social and cultural side (worldview, personality, contacts), 3) close two-way relationship between biological and cultural.

The biopsychosocial nature of human beings, as defined in the World Health Organization's definition of health, can be reduced to a biosocial nature without losing meaning. The psychological level in this case (without diminishing the importance of psychology) is the transition level, the door between the biological material processes of the body and the semantic, symbolic reality of society, i.e. communication [4]. The soul, psyche or anima, is processes of body animation, mental functions: thinking, intelligence, memory, emotions, mood, etc. Their filling is somehow symbolic, communicative, and they are realized due to biochemical mechanisms of muscle contraction, isolation of neurotransmitters, bioelectricity.

Medicine of the turn of the XX-XXI centuries was purely biologic [5]. This is easy to understand,

**Table 1**

**Doctor's competencies according to Federal standards (adapted from [1, 2])**

| Competency level | Formulation |
|---|---|
| HE FSES project “3 ++” with occupational standards | |
| Universal | Ability to analyze and take into account the diversity of cultures during intercultural interaction |
| | Identify and implement the priorities of their own activities and ways to improve it on the basis of self-assessment and lifelong learning |
| | Maintain an adequate level of physical fitness |
| Current HE FSES | |
| General cultural | Ability to use philosophical knowledge to form a worldview |
| | Ability to take social and ethical responsibility for decisions made |
| | Willingness to self-development, self-actualization, self-education, use of creative potential |
| | Willingness to work in a team, to tolerate social, ethnic, religious and cultural differences |
| General occupational | Ability and willingness to implement ethical and deontological principles |
| | Ability and willingness to analyze the results of own activities to prevent mistakes |
| Occupational | Willingness to engage in educational activities to address risk factors and develop healthy lifestyle skills |

**Note:** HE FSES — Higher Education Federal State Educational Standard.

because the rapid development of natural sciences has overshadowed the slow and contradictory growth of human understanding of oneself through philosophy, culturology, sociology, psychology and art. Nevertheless, medicine as an aid to a human being requires work with both biological and cultural parts of it. Within clinical specialties, there is probably a moment of dichotomy: either we persist in developing the humanitarian competence of the physician, or we divide medical practice into two types — one that implies such competencies and the other that does not.

The conservative way in which the scientific and pedagogical community is following now will require a renewal of approaches to the formation of humanitarian competencies among doctors (and among the first — cardiologists taking care of patients with psychosomatic pathology [6]). Another way is to realize that it is impossible to embrace the entire complexity of biosocial interrelationships, and to identify clinicians who are able and unable to work with a person. This recognition of defeat is possible, but maybe it is a requirement of evolution, a new, modern view of medical care. “Medical doctor” and “biomedical doctor”, for example, the names of two types of clinicians that differ by way of working with a patient. The first one suggests a high level of communicative and social skills, the second one — only actions in the field of pharmacology, surgery, diagnostic methods, physiotherapy with minimal and formal communication.

The conservative way is more comfortable. If you follow it, what are the competences of a clinician capable of working with the social self of a patient no less effectively than with the biological processes of his body, taking into account the close relationship between the social and biological aspects?

When interacting with a sick person or a patient as part of primary prevention, the doctor deals with both the "pure" biology and the symbolic reality of this individual. The administration of the drug, not to mention surgical intervention, is nothing but the effect on the biology of the patient. But the psychological processes of experience (negative and positive emotions, mood) are biochemical states. It is associated with a reflection on social life. Cognitive science explores "embodied cognition" [7]. There is plenty of evidence that emotions influence the development of chronic diseases and their exacerbation. Stress is a typical example of a body's biochemical response to understanding social reality: stress factors such as changes in currency exchange rates and job losses.

The biological response is well studied, and it is quite simple in nature. The processes of experience are much more complex — semantic and symbolic processes. They are complicated simply because, unlike biological (natural science) processes, it is impossible to generalize, make a sample and calculate reliability. They are purely individual and require skills of interpretation according to the laws of humanitarian knowledge. Although some natural scientists do not consider humanitarian knowledge to be scientific in principle, it is not so much a matter of designating it as of its essence and practical significance. As such, science itself is only one way to know and change the world [8]. Medicine, on the other hand, is a broader science that has the reality of life with its subject matter, including notions that are imperceptible (fate, god, soul, etc.), but that are important for the patient and, as a result, through experience, affect his or her coping with the disease. Working with a person (alive, in the mind), one cannot help but understand him, decode the factors influencing his adherence to the disease, his attitude to the situation of the disease, his ability to change his lifestyle due to the medical situation.

Psychology is partly responsible for the study of the human being's social. This science has both strict biological fields (neuroscience) and social fields (consultative psychology). Doctor's humanitarian competences are at least psychological competences. But they are not enough for effective work. Moreover, the work with the individual is done with the help of another person, and the clinician cannot abstract his or her personality from the patient's personality, in which case he or she becomes a "biomedical doctor" (see above). Therefore, the key humanitarian competence is the skill and ability to work internally, build awareness, reflexivity, constructive self-criticism, and the ability to change yourself.

Self-identification is a person's experience of the self in relation to social categories. For example, fitness as a muscle building represents the realization of a certain image of body, which is perceived as a standard. And for one man the aim will be the hypertrophy of the muscles as such, for the other — the achievement of "Greek" proportions and relief. In both cases, the processes take place at the somatic level and a person may eventually become a cardiologist's patient due to, for example, arterial hypertension or cardiomyopathy. An even simpler example is

alcohol consumption as a social practice. If a person's self-identification requires recognition in a certain social group, he or she will be forced to consume an excessive amount of alcohol in a feast; the classic situation — "do you respect me? — then drink". When working with such a patient, it is not enough to simply forbid the harmful action, not even to scare with consequences (the reaction may be the opposite, for example, depression, negativism), you need to be able to understand his motivation. Motivation comes from values, value is conditioned by the correlation of the image of the self with the wishful one in the society, and the wishful one is a construct based on the whole human experience.

The above is enough for a somatic doctor to draw a conclusion about the complexity and potential infinity of working with an individual as a person, the social self. But the matter is not in the complexity of this knowledge. The main feature is a qualitative difference of such knowledge. It is non-generatable, unrepeatable, irreplaceable. It is interpretive, and therefore requires tools for analysis: knowledge of history and philosophy of culture, knowledge of psychology, skills to communicate in order to understand the person, not only to collect data. For a "biomedical doctor", pain as a symptom is only a "talking biology," which has a process that manifests itself in complaints of pain. For a clinician, pain is also the patient's experience, his or her perceptions and fears, projection on life, the question "for what?" or "will it always be so now? In doing so, the doctor does not have to suffer pain together with the patient; the ability of a conscious attitude allows one to be involved in person's problem without crossing the boundaries of oneself.

The importance of quality methodology in cardiology was discussed in the article [6]. In fact, this is how the old clinical school returns to a new phase of medical development. Simple references to the full collection of anamnesis, to the correct conversation with the patient, to the consideration of personal traits will sound conservative and sentimental today, if they are not supported by modern ideas about the biosocial relationships, ways to understand the cultural part of the patient, and the doctor himself — to construct his own social identity.

Traditionally, the "non-biological part" of the patient is devoted to the specialty and field of medicine with the word root of "psych-" in its name: psychiatry, psychosomatics, psychocardiology. Although they nominally deal with processes of psychological level, any manifestation of such processes consists in felt, perceived and interpreted symbols. Bio-psychological processes are not available until they are expressed and become psychosocial phenomena. Already V.A. Gilyarovsky said "every epoch has its own psychiatry" [9]. Extrapolating this idea into psychocardiology, stress, harmful habits, and unhealthy lifestyles as cardiovascular risk factors lies in the information environment. It means that the etiopathogenetic tangle has to be unraveled from above. Psychosomatics, psychocardiology, if not redefined, acquire a different level of work. This can be looked at even more widely, because all noninfectious pathology somehow begins with psychosocial risk factors.

Patient-centered care is attached to such doctor's work, with elements of quality methodology. Its simplest attitudes always require positive mood, empathy, respect, constructive communication, joint decision making and tolerant information sharing.

Finally, decision making in ethically complex situations requires the physician to be an ethical subject, i.e. a person capable of understanding and solving each unique situation. Especially if the legal framework is not sufficiently detailed.

Where to find the resource to do this — both formally and substantively? Obviously, it's about humanitarian competencies. Humanitarian — according to the vocabulary definition, refers to society, human beings and their culture (as opposed to the sciences of nature). The following competences can be defined as:

**Internal work** — the ability to reflect on one's feelings, one's attitude towards another person (colleagues, patients, relatives of patients), to the situation; find the reasons for their attitude to the situation, their feelings, analyze and rationalize them; the tendency to fulfill the postulate "doctor, heal thyself."

**Situational search and interpretation** — the ability to ask questions about hidden meanings and sources of what is happening — both locally, in the situation of assistance, and globally; to find codes with which the information is presented, its possible distortion and substitution.

**Communicative competences** — the ability to conduct a dialogue with patients, their relatives, colleagues, in a constructive manner, without creating situations of misunderstanding, conflict; to be aware of their own experiences and meanings generated by communication; to express themselves in the manner necessary for effective communication, taking into account the phenomenon of power of the doctor as a representative of medicine and health care [10].

**Ethical competences** — the ability to highlight the ethical element of a situation, to distinguish between good and bad, right and wrong; to obtain additional information necessary to make ethically loaded decisions.

**Positive health development** — understanding of the structure of health (wellbeing) at the socio-cultural level; ability to interpret socio-cultural determinants of disadvantage and find ways to resolve them (it should be added that the considered standards and draft standards of education of the levels of specialization and residency considered do not reveal competencies related to health as an interdisciplinary concept according to WHO).

The development of humanitarian competencies among students and physicians in postgraduate and continuing education is possible with the proper "tuning" of humanitarian and psychological disciplines. The most important is the essential component — the formation of a way to think analytically, to use different points of view to understand the same phenomenon. In today's era of information abundance, the key skill is to preserve one's self-identification as autonomous and independent of external information influences as possible. For a doctor as one of the most important actors in the lives of other people, this is especially important.

**Conflicts of Interest:** nothing to declare.

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# The role of muscle tissue in the pathogenesis of chronic heart failure — the potential of exposure (FORMA study)

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**Aim.** To determine whether the skeletal muscle of patients with chronic heart failure (CHF) retains the ability to regenerate and grow; to compare the effectiveness of long aerobic trainings, calculated by an individualized method, and conventionally calculated trainings ($VO_2$peak values), in relation to the severity of heart failure, exercise tolerance (ET), and ergoreflex activity (ERGO).

**Material and methods.** The study included 297 patients with stable III functional class (FC) CHF, receiving optimal therapy. The presence of heart failure was found in all patients at least 6 months before the start of the study (age — 18-65 years, body mass index (BMI) — 19-28 kg/height, $m^2$. Initially, the study performed a cardiorespiratory test (CRT) with an assessment of gas composition, acid-base balance of the blood and ERGO activity. Patients were randomized into 2 groups: experimental (EG) and control (CG). For EG, based on the determination of the lactate threshold (LT), after 1 and 3 months the CRT was repeated and the training walking mode was dynamically recounted according to the new LT level. For CG, the training walking mode was calculated based on the $VO_2$peak values. All patients trained for 6 months. At the end of the training, diagnostic CRT was performed, and the activity of EGO was evaluated. Eleven patients with CHF and 3 healthy donors before the start of the training underwent a biopsy of the gastrocnemius muscle.

**Results.** It was shown that the potential for muscle differentiation of satellite skeletal muscle precursor cells obtained from patients with CHF with a reduced ejection fraction (HFrEF) does not differ in vitro from the potential of satellite cells of healthy donors. After 6 months of training, the severity of CHF decreased to FC II in 75% of EG patients, and among CG patients — in 44%; the main indicators of the stages of compensatory mechanisms activation during physical exertion ($VO_2$LT and $VO_2$peak) in EG increased more than in the CG (10,8±0,4, 18,7±0,7 ml/min/kg and 9,5±0,8, 15,3±0,9 ml/min/kg, with $p_1<0,01$, $p_2<0,05$, $p_3<0,01$, respectively).

**Conclusion.** In vitro, the potential for muscle differentiation, regeneration and growth of satellite skeletal muscle precursor cells obtained from patients with HFrEF does not differ from the potential of satellite cells of healthy donors. Aerobic training in patients with III FC chronic heart failure calculated by definition of LT, relating to safety is not worse than the results calculated by the level of $VO_2$peak. Aerobic training in patients with III FC chronic heart failure calculated by definition of LT, compared with the usual mode of training walking, significantly reduce the activity of ergoreflex, increase ET, reduce the severity of CHF. In patients with III FC CHF, training walking for more than 1,5 hours/day determined by the level of LT, contributes to the development of physiological reverse myocardial remodeling to a greater extent than aerobic training calculated by the conventional method.

**Key words:** heart failure, long aerobic training, ergoreflex, inversion of myocardial remodeling, skeletal muscle satellite cells, muscle tissue regeneration.

**Conflicts of Interest:** nothing to declare.

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The prevalence of heart failure (HF) in the Russian Federation has reached the epidemic [1, 2]. By evidence-based medicine, effective methods to combat this pathology were developed, including basic medications: angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (ARA II), angiotensin receptor-neprilysin inhibitors (ARNi), beta-blockers (BB), mineralocorticoid receptor antagonists (MCRA). However, to date, it has not been possible to stop the rapid increase in the number of rehospitalizations due to decompensated HF, which significantly burdens the economies of the countries.

Despite the inhibitory effect of BB, ACE inhibitors, ARA II, ARNi, MCRA, neurohumoral activation in HF is increased due to continuous peripheral afferent stimulation (enhanced ergoreflex activity).

One of the possible points of application for HF stabilization is striated muscle tissue. Stimulation of molecular mechanisms for skeletal muscle regeneration, including physical rehabilitation, is a promising strategy to reduce muscle dysfunctions. Therefore, it seems relevant to determine whether the skeletal muscles in HF patients retain their ability to regenerate and grow. Data on such studies was not found.

As any organ or tissue in HF, skeletal muscles suffer from a lack of oxygen and nutrients. There are following differences: muscle tissue is the largest organ by mass in human — 40-45% of body weight; muscles have a special feedback system called "ergoreflex".

Between the skeletal muscles on the one hand and the vasomotor and respiratory centers on the other hand, there are neurogenic connections that are mediated by ergoreceptors. Ergoreceptors are myelinated and non-myelinated afferent nerve fibers in the skeletal muscles, sensitive to all mechanical and metabolic changes in muscle fibers. Ergoreceptors play a major role in feedback control to maintain a balance between muscle load intensity and energy for this. Ergoreflex is a defensive mechanism of the body in response to metabolite accumulation in muscle fiber, aimed at removing metabolites and enhancing aerobic oxidation. In response to the muscle metabolic state, ergoreceptors modulate the intensity of muscle perfusion and the cardiorespiratory response to physical activity in order to meet the metabolic needs of contracting muscles. So, there is an increase in ventilation and a number of circulatory changes due to an enhanced sympathetic nervous system (SNS) activity — increase of heart rate and blood pressure (BP), contraction of the resistance vessels (Fig. 1).

Thus, skeletal muscle is not only the largest organ by mass in the human body, but also an organ that controls the activity of the cardiovascular and pulmonary systems by means of ergoreflex (Fig. 1). However, data on effective influencing methods is currently contradictory. The only and most physiological way to reduce the ergoreflex activity is exercise training (ET).

Physical therapy (PT) in HF patients should be used to improve exercise tolerance and quality of life, reduce the number of hospitalizations for decompensated HF [1, 2]. Currently, individual selection of the type, duration and intensity of physical activity in HF patients is an urgent problem.

There were following aims of the study: 1) to determine whether the skeletal muscle in HF patients retains the ability to regenerate and grow; 2) to compare the effectiveness of individualized and conventional (based on $VO_2$peak) approaches to selecting exercise mode, in relation to the severity of HF, exercise tolerance, and ergoreflex activity.

## Materials and methods

Gastrocnemius muscle biopsy and assessment of muscle-resident cells. Eleven HF patients (mean age 54±12,5 years, body mass index (BMI) — 26,5±6,4 kg/m$^2$, left ventricular ejection fraction (LVEF) 26,4±1,4%) and 3 healthy donors underwent gastrocnemius muscle biopsy. The preparation of primary muscle-resident cell cultures enriched in satellite cells was performed according to the standard methods [3]. Preparing Geltrex-coated (Invitrogen, USA) culture dishes was performed for 1,5 h in a $CO_2$ incubator at +37°C in a Dulbecco's Modified Eagle's medium (DMEM) in a ratio of 1:100. The culture

medium was changed every other day. Myogenic differentiation of cells was performed according to the standard methods [3, 4] when cultured in a differentiation medium consisting of a basic culture medium (α-MEM) (PanEco, Russia) with the addition of 1% L-glutamine (Invitrogen, USA), 1% Penicillin-Streptomycin (Invitrogen, USA) and 2% horse serum (Gibco, USA). The primary medium was replaced with a differentiation one when subconfluent state of the culture was observed. During immunocytochemistry, the cells were washed with phosphate buffered saline (PBS) and fixed with 4% paraformaldehyde at +4°C for 10-15 minutes, washed with PBS, incubated with 0,2% TRITONx100 for 5 minutes, washed with PBS, blocked with 15% fetal calf serum for 30 minutes (Gibco, USA) in PBS. Incubation with primary and secondary antibodies were perfomed according to the manufacturer's instructions (MF20 antibodies to the myosin heavy chain (MHC MF20), myogenic factor 5 (Myf5), mitofusin-1 (Mfn1), PAX transcription factors, R&D BioSystems, USA). Immunophenotyping was performed by CytoFLEX flow cytometer (Beckman Coulter). Data was analyzed using CytExpert 2.0 software (Beckman Coulter).

Isolation of ribonucleic acid (RNA), synthesis of complementary deoxynucleic acid (cDNA) and real-time polymerase chain reaction (PCR). Total RNA was isolated using ExtractRNA reagent (Evrogen, cat.no BC032, Russia). cDNA was synthesized from 500 ng total RNA using a reverse transcription kit (Molove, SK021, Russia). Quantitative gene expression was performed using qPCR-HS SYBR + ROX (Evrogen, cat.no. PK156, Russia). Data of qPCR are presented as arbitrary units of mRNA expression normalized to GAPDH expression and expression levels in a reference sample.

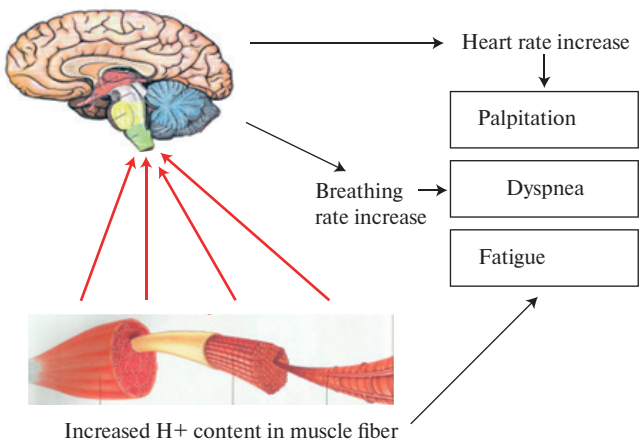


**Fig. 1.** The role of muscle tissue in HF pathogenesis.

**Statistical analysis** was performed using GraphPadPrism7 software. All data were analyzed by at least three biological replicates and presented as mean±SEM.

**Safety and effectiveness of different exercise methods** was assessed as part of the FORMA study. A prospective, randomized study was performed in accordance with Good Clinical Practice guidelines and the principles of Declaration of Helsinki; the study protocol was approved by the ethics committee of the Almazov National Medical Research Center. There were following inclusion criteria: symptoms of class III HF; stable clinical status for at least 2 weeks before inclusion in the study; age — 18-65 years; body mass index (BMI) — 19-28 kg/m$^2$; completed informed consent; the ability to perform cardiorespiratory test (CRT); LVEF <45%; administration of ACE inhibitors/ARA II/ARNi, BB, MCRA, diuretics; patient education during hospitalization at Almazov National Medical Research Center; follow-up monitoring of HF patients by a cardiologist. Exclusion criteria were moderate and severe chronic obstructive pulmonary disease (COPD), myocardial infarction (MI), pulmonary embolism (PE), surgeries over the past 6 months, severe cognitive disorders, low adherence treatment.

The endpoints of the study were changes in the HF severity, exercise tolerance ($VO_2$peak), ergoreflex, and myocardial contractile function (LVEF, LV end-diastolic dimension (LV EDD), LV end-systolic dimension (LV ESD)).

**Clinical characteristics of patients.** The study included 297 patients with stable class III HF, which was established at least 6 months before the study. Patients were randomized into two groups: the experimental group (EG) — 237 patients with class III HF (age 18-65 years, BMI 19-28 kg/m$^2$) and control group (CG) — 60 patients with HF (age 18-65 years, BMI — 19-28 kg/m$^2$). After 4-6 weeks of exercise, 55 EG patients on their own initiative gradually increased the duration of daily walk to 1,5-2 hours; this subgroup of patients (EGlong) was allocated for additional analysis (Table 1).

Therapy did not differ significantly between groups. Results of clinical and instrumental examinations are presented in Table 1.

The study progress is presented in Table 2. Initially, the subjects underwent a submaximal CRT with a simultaneous assessment of gas composition and acid-base status of the blood (Table 2).

For each EG patient, the exercise mode of walk was estimated according to the CRT results based on the lactate threshold (LT) determination; after 1 and

**Table 1**

**Clinical characteristics of patients**

| Parameter | Experimental group | | | Control group | P | | | |
|---|---|---|---|---|---|---|---|---|
| | EG | EGpres | EGlong | | EG and CG | EGpres and EGlong | EGpres and CG | EGlong and CG |
| Demographic characteristics | | | | | | | | |
| Total number of HF patients, n | 237 | 182 | 55 | 60 | | | | |
| Age, years, M±m | 53,1±4,2 | 52,3±5,0 | 57,3±6,5 | 51,0±6,1 | >0,05 | <0,05 | >0,05 | <0,05 |
| Men, n (%) | 176 (75) | 133 (75) | 52 (93) | 36 (60) | <0,05 | <0,05 | >0,05 | <0,05 |
| BMI, kg/m$^2$, M±m | 27,5±0,5 | 27,0±0,9 | 28,1±1,3 | 26,2±2,8 | >0,05 | <0,05 | >0,05 | <0,05 |
| Etiology of HF | | | | | | | | |
| CAD, n (%) | 158 (67) | 129 (70) | 29 (53) | 35 (58) | >0,05 | <0,05 | <0,05 | >0,05 |
| DCMP, n (%) | 79 (33) | 53 (30) | 26 (47) | 25 (42) | >0,05 | <0,05 | <0,05 | >0,05 |
| Concomitant pathology | | | | | | | | |
| AF, n (%) | 29 (12) | 22 (13%) | 7 (11%) | 6 (10%) | >0,05 | >0,05 | >0,05 | >0,05 |
| Anemia, n (%) | 12 (5) | 10 (5%) | 2 (4%) | 5 (8%) | <0,05 | >0,05 | <0,05 | <0,05 |
| COPD, n (%) | 85 (36) | 67 (35%) | 18 (30%) | 24 (40%) | <0,05 | <0,05 | <0,05 | <0,05 |
| High tech treatments | | | | | | | | |
| CRT, n (%) | 52 (22) | 41 (23%) | 11 (20%) | 9 (15%) | <0,05 | >0,05 | <0,05 | <0,05 |
| CABG, n (%) | 73 (30) | 61 (34%) | 12 (23%) | 19 (28%) | >0,05 | <0,05 | <0,05 | <0,05 |
| Left ventricular ejection fraction | | | | | | | | |
| LVEF,% | 30±1,3 | 29±1,5 | 30±3,5 | 32±3,3 | >0,05 | >0,05 | >0,05 | >0,05 |
| Medication, maximum tolerated doses | | | | | | | | |
| ACE inhibitors/ARA II/ARNi, n (%) | 237 (100) | 182 (100) | 55 (100) | 60 (100) | >0,05 | >0,05 | >0,05 | >0,05 |
| Beta-blockers, n (%) | 237 (100) | 182 (100) | 55 (100) | 60 (100) | >0,05 | >0,05 | >0,05 | >0,05 |
| MCRA, n (%) | 212 (90) | 163 (90) | 51 (93) | 54 (91) | >0,05 | >0,05 | >0,05 | >0,05 |
| Diuretic therapy | | | | | | | | |
| Diuretics, n (%) | 237 (100) | 182 (100) | 55 (100) | 60 (100) | >0,05 | >0,05 | >0,05 | >0,05 |

**Abbreviations:** BMI — body mass index, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease, CRT — cardiac resynchronization therapy, CABG — coronary artery bypass grafting, LVEF — left ventricle ejection fraction, CG — control group, EG — experimental group, EGpres — EG subgroup with preserved load during physical rehabilitation, EGlong — EG subgroup with long-lasting exercise.

3 months the CRT was repeated and on the basis of the newly obtained LP values, the mode was re-estimated (walking speed was 95% of the LT speed) [5, 7]. Patients trained for 6 months. At the end of the exercise, a diagnostic CRT was performed. CG patients performed walking at the level of 55% $VO_2$peak 3 times/week. Echocardiography was conducted using Philips iE-33. We used one- and two-dimensional scanning modes, by which the transverse dimension of the left atrium (LA), EDD, ESD, and LVEF were assessed. The CRT was performed using treadmill (GE Medical Systems Information Technologies) and Oxycon Pro system (Jeger, Germany).

**Venous blood lactate concentration at rest and during physical exertion.** Before the CRT, the catheter was inserted into the ulnar vein. Blood sampling was carried out initially and every minute during the physical exertion. Venous blood lactate concentration was evaluated by i-STAT Portable Clinical Analyzer (Abbott, USA) using CG4 cartridge kits. LT was recorded at the time of the beginning of

**Table 2**

**Progress of FORMA study**

| Initially | 1 m | 3 m | 6 m |
|---|---|---|---|
| Cardiorespiratory test | + | + | + |
| Echocardiography | + | | + |
| Assessment of ergoreflex | + | | + |
| Assessment of HF class | + | + | + |
| Assessment of adverse events | + | + | + |

blood lactate concentration increase [5-7]. The assessment of ergoreflex was carried out by post-exercise regional circulatory occlusion (PE-RCO) [8]. During the test, diastolic blood pressure (DBP) was measured; ventilation and gas exchange rates were recorded. The difference between DBP, carbon dioxide ventilatory equivalent ($VE/VCO_2$), minute ventilation (VE) after a three-minute occlusion (+PE-RCO) and the recovery period without occlusion (–PE-RCO) was calculated; percentage ratio of these values was estimated.

**Statistical analysis** was performed using Statistica 6.0 software. All data were analyzed by at least three biological replicates and presented as mean+SEM. Comparison of mean values was performed using nonparametric statistics (Mann-Whitney U-test). The chi-squared test and the F-test were used to identify confidence in contingency tables. The significance level was $p<0,05$.

## Results

**Examination of stem cell population obtained by skeletal muscle biopsy.** After isolation of cells and several days of in vitro expansion, we analyzed the expression of surface markers: CD56, CD105, CD166, CD146, CD73, CD140a, CD140b; CD45 was used as a negative control (Fig. 2). We showed that the vast majority of the isolated cells were CD56-positive (marker of satellite cells) and CD45-negative (marker of hematopoietic cells). We also found that a significant fraction of cells expressed stromal markers CD105, CD166 and CD73, and only a small fraction of cells was positive for markers CD146, Cd140a and CD140b. The high level of expression of stromal markers in the population was most likely associated with contamination of the satellite cell fraction with the stromal cell fraction of muscle tissue. Therefore, an immunocytochemical analysis of the obtained samples was carried out, which confirmed the expression of the satellite cell markers Pax7 and Myf5 (Fig. 3A). The results of a quantitative analysis of immunocytochemical staining and expression of mRNA markers of satellite cells and myoblasts are shown in Fig. 3. The level of mRNA expression of both Myf5 and Pax7 was high and did not differ significantly between samples of healthy donors and patients with HF. The percentage of Myf5+ and Pax7+ cells also did not differ significantly in the samples. The results of the stimulation of differentiation showed that cells obtained from both healthy donors and HF patients have a similar potential for muscle differentiation in vitro. Fig. 4 shows the myotubes obtained after stimulation of muscle differentiation of satellite cell samples in vitro. The fusion coefficient did not differ significantly between the groups and amounted to 19±7% and 23±5% in the samples of healthy donors and HF patients, respectively.

**Comparison of safety and effectiveness of conventional and individualized approaches to selecting exercise mode.** Of 297 patients, 25 people discontinued participation in trial: 8 EG patients, 17 — CG ($p<0,05$); there were following reasons: unwillingness to continue exercise (n=10), heart transplantation (n=6), non-HF hospitalization (n=4), 3 — hospitalization due to decompensated HF after URTI. Thus, 229 EG and 43 CG patients completed the study.

After 6 months of exercise, the severity of HF decreased to class II in 75% of patients from EG, and among control patients — in 44%; the main indicators of the stages of the inclusion of compensatory mechanisms in FN ($VO_2$LP and $VO_2$peak) in the EG increased more than in the CG (10,8±0,4, 18,7±0,7 ml/min/kg and 9,5±0,8, 15,3±0,9 ml/min/kg, in $p1<0,01$, $p2<0,05$, $p3<0,01$, respectively).

After exercise, in OG patients there was a more pronounced decrease in the ergoreflex activity compared to CG patients: DBP — by 40%, VE in OG — by 53%, $VE/VCO_2$ — by 38%, and in CG — by 21%, 23% and 15%, respectively ($p<0,05$) (Table 3).

Table 4 presents echocardiography changes in the studied patients before and after physical rehabilitation. In the EG, LV EDD, LV ESD, LVEF and left atrium dimension were significantly improved. In the CG, there was a significant increase in LVEF; LV EDD, LV ESD, and left atrium dimension were not significantly improved. Against the background of long-lasting aerobic exercise, patients from the EGlong subgroup showed a significant decrease in the end-systolic and end-diastolic volumes of the LV and LA, as well as a more pronounced LVEF increase than in the EG with preserved load (EGpres) and CG (Table 4).

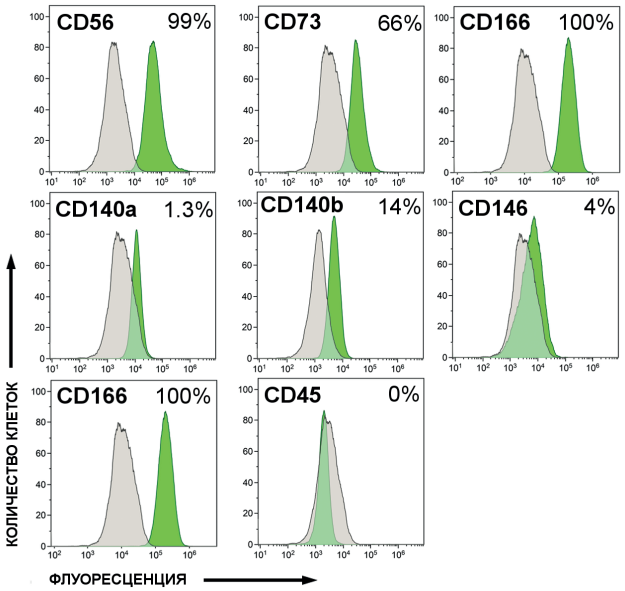


**Fig. 2.** The results of immunophenotyping of satellite cells isolated from human skeletal muscle and cultured *in vitro*.
**Note:** histograms represent the immunophenotype of the obtained cells (n=3 in each group).

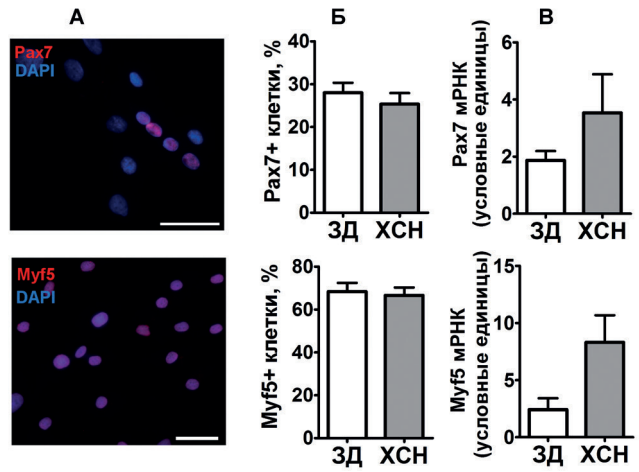


**Fig. 3 (A, B, C)**. Analysis of expression of the satellite cell markers Pax7 and Myf5.
**Note:** A. Immunohistochemical staining confirmed the expression of the markers Pax7 and Myf5 in the selected population. Representative photographs are presented; B. Results of a quantitative analysis of immunohistochemical staining; C. Results of analysis of the expression of Pax7 and Myf5 mRNA by real-time PCR.
**Abbreviations:** HD — healthy donors, HF — patients with heart failure.

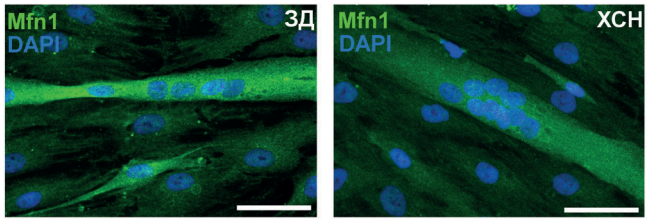


**Fig. 4.** Immunocytochemical staining of differentiated myotubes.
**Note:** representative photographs are presented. Myotubes are visualized by anti-mitofusin antibodies.
**Abbreviations**: HD — healthy donors, HF — patients with heart failure.

## Discussion

In HF, systemic metabolic changes are accompanied by muscular wasting, which in turn causes deterioration in physical performance and quality of life [1, 2, 5-6].

The aim of the first part of this project was to determine whether the skeletal muscle in HF patients retains the ability to regenerate and grow. The results of the study demonstrated that striated muscle cells of patients with class III HF do not have significant differences with cells obtained from healthy donors. They have similar potential for muscle differentiation in vitro and show a high potential for restoration of muscle precursor cells.

Thus, the skeletal muscle satellite cells under favorable conditions can contribute to the restoration of muscles injured due to HF. The exact molecular mechanisms of skeletal muscle restoration in HF patients have to be investigated. It is obvious that novel therapeutic strategies should be aimed at activating the regeneration potential of satellite cells, which may be partially realized by physical exercise.

The results of applying different exercise modes are reflected in the second part of this study. In 2017, Russian recommendations for the appointment of physical training for patients with chronic heart failure were published [1]. It was proposed to select the regime of physical rehabilitation empirically, based on the six-minute walk test (6MWT) or $VO_2$peak. Nevertheless, the 6MWT results largely depend on the motivation of patient and doctor, concomitant pathology and many other factors. Therefore, a physical rehabilitation program estimated by 6MWT can be not accurate [1, 6]. $VO_2$peak is also highly specified by the patient's motivation [1, 6]. Some aspects in determining the exercise regimen for HF patients remain open: there are no uniform principles for controlling the adaptation to physical activity; principles for planning the effective, safe and personalized exercise has not been fully developed [1, 6].

In 2012, we proposed the selection of the walking training mode based on the LT determination [7, 9]. The advantage of this approach is to increase the accuracy of determining the reserves of adaptation to physical activity. This method, in

**Table 3**

**Parameters of ergoreflex activity in patients with class III HF before and after exercise**

| Parameter | Initially | | | After 6 months of exercise | | |
|---|---|---|---|---|---|---|
| | EG | CG | p | EG | CG | p |
| DBP changes, mm Hg, % | 86,5 | 89,7 | >0,05 | 56,2 | 72,1 | <0,001 |
| VE changes, l/min, % | 93,8 | 92,7 | >0,05 | 48,5 | 69,5 | <0,001 |
| VE/VCO2 changes, % | 33,9 | 32,2 | >0,05 | 20,7 | 28,2 | <0,001 |

**Note:** p — significance of cardiorespiratory test differences in HF patients before and after exercise.
**Abbreviations:** DBP — diastolic blood pressure, VE — minute ventilation, $VE/VCO_2$ — carbon dioxide ventilatory equivalent.

**Table 4**

**Echocardiography in patients with class III HF before and after exercise**

| Parameter | LA, sm | | LV EDD, sm | | LV ESD, sm | | LVEF, % | |
|---|---|---|---|---|---|---|---|---|
| | Before PR | After PR | Before PR | After PR | Before PR | After PR | Before PR | After PR |
| EG | 5,52±0,09 | 5,31±0,05* | 6,37±0,08 | 6,10±0,09** | 5,91±0,12 | 5,68±0,08* | 30±1,3 | 39±1,7** |
| EGpres | 5,51±0,22 | 5,33±0,05* | 6,39±0,15 | 6,13±0,11** | 5,95±0,18 | 5,75±0,11* | 29±1,5 | 37±2,1* |
| EGlong | 5,54±0,29 | 5,25±0,05** | 6,36±0,19 | 6,05±0,28** | 5,93±0,30 | 5,55±0,18** | 30±3,5 | 41±2,9** |
| CG | 5,46±0,38 | 5,41±0,35 | 6,32±0,37 | 6,27±0,25 | 5,91±0,32 | 5,87±0,29 | 32±3,3 | 36±4,1* |

**Note**: p — statistical significance: * -– p<0,05, ** — p<0,001.
**Abbreviations:** PR — physical rehabilitation, LA — left atrium, LV EDD — left ventricle end-diastolic dimension, LV ESD — left ventricle end-systolic dimension, LVEF — left ventricle ejection fraction, EG — experimental group, EGpres — EG subgroup with preserved load during physical rehabilitation; EGlong — EG subgroup with long-lasting exercise, CG — control group.

comparison with the previous ones, allows developing physical rehabilitation programs for any cardiovascular patients. [5, 7, 9]. This study demonstrated the safety and effectiveness of present approach in class III HF patients. Its using allows to avoid the fatigue and, therefore, to prescribe a longer physical exercise. Described method makes it possible to softly increase the load based on the LT re-determination. As a result, there is a greater decrease in the ergoreflex activity in the EG, followed by decrease in neurohumoral activation [5]. Also longer exercise duration can increase the number of mitochondria and exercise tolerance compared with conventional approaches where the time and load are strictly fixed. This is confirmed by the fact that in patients with LT-dependent exercise load, the tolerance increased more significantly, and in patients with >1,5 hours/day exercise, reverse myocardial remodeling was observed.

**Limitations:** a relatively small number of patients in the group of long-lasting exercise and multicenter design.

## Conclusion

1) *In vitro*, the potential for muscle differentiation, regeneration and growth of satellite skeletal muscle precursor cells obtained from patients with HF with reduced EF does not differ from the potential of satellite cells of healthy donors.

2) Safety of aerobic exercise in patients with class III HF estimated by LT definition is equal with exercise estimated by the level of $VO_2$peak;

3) Aerobic exercise in patients with class III HF estimated by LT definition, compared with the conventional approach, significantly reduce the activity of ergoreflex, increase exercise tolerance and reduce the HF severity.

4) In patients with class III HF, walking training >1,5 hours/day estimated by the LT level, contributes to the development of physiological reverse myocardial remodeling to a greater extent than aerobic exercise selected by the conventional method.

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**Conflicts of Interest:** nothing to declare.

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