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Methods of study in cardiology

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Biomarkers of inflammation in patients with myocardial infarction and heart failure with preserved and mid-range ejection fraction: 5-year prospective follow-up

Musikhina N. A., Petelina T. I., Kostousova A. I., Gapon L. I., Gorbatenko E. A., Bessonov I. S.

Aim. To evaluate the effect of biomarkers of inflammation on the long-term prognosis in patients with myocardial infarction (MI) and heart failure (HF) with preserved and mid-range ejection fraction according to a registry of percutaneous coronary interventions (PCI).

Material and methods. A total of 135 patients with MI included in the PCI registry in 2012-2013 were examined. Group 1 included 89 patients with HF with mid-range ejection fraction (HFmrEF) — 40-49%; group 2 included 46 patients with HF with preserved ejection fraction (HFpEF) — ⩾50%. Biomarkers of inflammation were determined at admission to the hospital, after 12 and 60 months.

Results. Eighteen people died during the follow-up period. The survival rate of patients in the compared groups after 60 months did not differ (group 1 — 85,0%; group 2 — 89,1%, p=0,492). Mortality predictors were the platelet count (HR, 1,011; 95% CI, 1,003-1,019; p=0,010), homocysteine level (HR 1,172; 95% CI, 1,008-1,364; p=0,040), MMP-9 >249 ng/ml (HR, 7,052; 95% CI, 1,346-36,950; p=0,021). In both groups there was a decrease in survival in patients with high levels of MMP-9 (>249 ng/ml). In group 1, mortality was higher among patients with platelet count >245*10^9/l. In both groups the levels of inflammatory markers exceeded the standard values for the entire period of follow-up. The dynamics of NT-proBNP, hs-CRP, TNF-α and homocysteine had a unidirectional pattern, in particular, a decrease in parameters after 12 months, followed by their increase after 60 months.

Conclusion. Levels of MMP-9, homocysteine, and platelets were the factors that influenced 5-year survival in the general group of patients after MI and PCI. In the group with HFmrEF, MMP-9 and platelets had a negative impact on the prognosis. In patients with HFpEF, reduced survival was associated only with high levels of MMP-9. The dynamics of markers of systemic inflammatory response and NT-proBNP indicates the prolonged inflammatory process in both groups of patients, persisting for 5 years after MI.

Keywords: myocardial infarction, heart failure, markers of inflammation, 5-year follow-up.

Relationships and Activities: none.

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Risk of cardiovascular events (CVE), especially death, remains high not only at the acute stage of myocardial infarction (MI) but also at later stages. Lately, the biochemical markers of system inflammation have been widely used when evaluating the forecast in acute coronary syndrome (ACS). They are of great importance in the pathologic physiology of the acute stage of MI.

Success in treating acute myocardial infarction (AMI) resulted in a growing number of patients with the signs of heart failure (HF) since in many of them MI is a starting point in developing HF with preserved ejection fraction (EF) ⩾50% (HFpEF) and reduced EF ⩽40% (HFrEF), which is associated with a high frequency of rehospitalizations and high death rate. Lately, in addition to distinguishing HFpEF and HFrEF, patients with mid-range EF (41-49%) (HFmrEF) have been differentiated. Patients with HFmrEF are so-called grey area, which is insufficiently known. Currently, there is no reliable method to stratify the risks of adverse events in HFpEF and HFmrEF [1]. The formation of left ventricular dysfunction takes place not only by involving neurohumoral systems but also with the participation of immune inflammation. It is assumed that myocardial injury with following remodeling, dilatation together with hypoxia results in the arousal of all main cytokine sources — cardiomyocytes, skeletal muscles, and immune competent cells. It is possible that the initial increase in cytokine secretion can be directly associated with the pathogenesis of diseases, conditioning HF, at the following stages of the course of which one or several specified mechanisms is engaged [2-4]. Consequently, determining biomarkers in this category of patients for assessing prognosis becomes increasingly significant.

The aim was to evaluate the effect of biomarkers of inflammation on the long-term prognosis in MI patients with HFpEF and HFmrEF according to a registry of percutaneous coronary interventions (PCI).

Material and methods

The paper presents data available from the PCI registry conducted within the period of 2012-2013 at the Tyumen Cardiology Center (branch of the Tomsk National Research Medical Center). The study was conducted in accordance with Good Clinical Practice standards and the Declaration of Helsinki. The study was approved by the local Ethics Committee. Before inclusion, a written informed consent was obtained from every participant. Based on 2007 Russian Society of Cardiology and 2011 European Society of Cardiology/American Heart Association guidelines, ACS was diagnosed in 359 people who entered the register. After coronary angiography, all patients were made PCI with stenting using X-ray system Philips Integris Allura (Holland). The study group included 135 people with ST-segment elevation (45,9%) and non-ST-segment elevation (54,1%) MI. Group 1 (n=89) and group 2 (n=46) consisted of patients with HFmrEF and HFpEF, respectively. Patients in the groups were of the same age (60,8±9,8 years and 59,2±9,3, p=0,468, respectively), sex and have the same comorbidities as hypertension, diabetes, chronic kidney disease, and obesity. The optimal medication therapy included the antiplatelet agents, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin-2 receptor antagonists, statins, as well as nitrates and diuretics when necessary. After 12±3,1 and then 60±4,3 months, we contacted with patients for medical examination.

Venous blood was collected at admission, after 12 and 60 months. Neutrophils, lymphocytes, platelets were determined using Mindray BC-5800 5-diff auto hematology analyzer (China). The following parameters were also determined: high-sensitivity C-reactive protein (hs-CRP, reference range, 0-3,0 mg/l) — by immunoturbidimetry with C-reactive protein hs kit (BioSystem, Spain) using Semi-automatic biochemical analyzer Clima MC-15 (Spain); interleukin-1β (IL-1β, reference range, 0-5,0 pg/ml), interleukin-6 (IL-6), IL-8, tumor necrosis factor-α (TNF-α, reference range 0-8,11 pg/ml) — sandwich form and homocysteine (HYC, reference range, 5,0-15,0 umol/l), N-terminal pro-brain natriuretic peptide (NT-proBNP) — solid-phase competition enzyme-linked immunosorbent assay using the IMMULITE 2000 System (Siemens Diagnostics, US); matrix metalloproteinase-9 (MMP-9, reference range, 20,3-77,2 ng/ml) — Bender MedSystems an eBioscience company, Austria; tissue inhibitor of metalloproteinase-1 (TIMP-1, reference range, 92-116 ng/ml) — Human TIMP-1 Elisa K.t Invitrogen (USA) using the Personal Lab analyzer (Italy).

Table 1

The impact on laboratory inflammatory markers on the five-year death rate in the general group of patients

Laboratory parameters	HR	95% CI	p
Platelets, 10^9/l	1,011	1,003-1,019	0,010
Homocysteine, μmol/l	1,172	1,008-1,364	0,040
MMP-9 >249 ng/ml	7,052	1,346-36,950	0,021

Abbreviations: CI — confidence interval, MMP-9 — matrix metalloproteinase-9, HR — hazards ratio.

Table 2

Comparative characteristics of laboratory parameters during follow-up

Parameters	Group 1 (n=89), (Me [25%; 75%])			Group 2 (n=46), (Me [25%; 75%])		
	Initially	After 12 months	After 60 months	Initially	After 12 months	After 60 months
NT-proBNP, pg/ml	976,74 [121,00; 736,50]	396,48 [100,62; 401,50]*	759,92 [84,90; 573,00]	558,86 [96,90; 489,00]	236,72 [64,90; 224,50]§	356,55 [70,30; 302,50]†§
IL-1β, pg/ml	3,87 [2,70; 4,55]	3,88 [3,13; 4,40]	2,53 [1,93; 2,76]††	3,64 [2,83; 4,43]	3,65 [2,78; 4,33]	2,34 [1,80; 2,52]††
IL-6, pg/ml	3,87 [1,55; 4,10]	2,03 [1,35; 2,52]	2,32 [1,79; 2,83]††	3,40 [1,47; 3,79]	2,55 [1,39; 2,37]*	2,24 [1,51; 2,82]†
IL-8, pg/ml	13,49 [8,55; 16,40]	15,63 [9,36; 19,50]	11,94 [7,92; 14,90]††	17,87 [10,30; 18,20]	15,88 [9,37; 18,70]	10,96 [7,82; 13,80]††
TNF-α, pg/ml	6,18 [4,65; 7,49]	4,89 [3,15; 5,97]	6,41 [4,64; 7,55]†	6,24 [4,37; 8,49]	4,70 [3,55; 6,12]	5,86 [4,61; 7,39]†
Homocysteine, umol/l	14,80 [12,25; 18,20]	12,23 [8,16; 15,45]*	16,05 [8,16; 15,45]†	13,45 [10,30; 15,90]	11,36 [8,32; 14,75]**	14,31 [10,92; 15,85]††
MMP-9, ng/ml	237,62 [140,25; 303,05]	179,11 [144,47; 211,49]	133,53 [92,80; 184,45]†	202,43 [139,40; 230,40]	190,89 [139,25; 217,05]	160,40 [100,50; 207,45]
TIMP-1, ng/ml	250,54 [187,90; 318,20]	252,25 [204,77; 313,40]	284,58 [204,77; 313,40]	249,27 [193,80; 294,05]	255,28 [203,22; 282,75]	255,33 [198,75; 310,65]
hs-CRP, mg/l	4,80 [1,54; 8,21]	2,14 [0,54; 2,12]**	4,34 [0,54; 2,12]	4,41 [0,76; 6,02]	2,30 [0,50; 2,64]*	4,13 [1,43; 4,82]

Note: * — p<0,05 difference between the initial indicators and after 12 months, ** — p<0,01 difference between the initial indicators and after 12 months, † — p<0,05 difference between the initial indicators and after 12 and 60 months, †† — p<0,01 difference between the initial indicators and after 12 and 60 months, § — p<0,05 difference between the indicators in compared groups.

Abbreviations: hs-CRP — High-sensitivity C-reactive protein, IL-1β — interleukin-1β, IL-6 — interleukin-6, IL-8 — interleukin-8, MMP-9 — matrix metalloproteinase-9, TIMP-1 — tissue inhibitor of metalloproteinase -1, TNF-α — tumor necrosis factor-alpha, NT-proBNP — N-terminal pro-brain natriuretic peptide.

The distribution was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as the arithmetic mean and standard deviation (M±SD); non-normally distributed variables — as a median, lower and upper quartiles (Me [25%; 75%]). Depending on the distribution, Student's t-test or Mann-Whitney test was used when comparing 2 independent groups and Friedman's test adjusted for multiple comparisons to assess the significance of differences. Qualitative variables are presented as relative frequencies (n, %). Comparison of these variables in 2 groups was performed using the chi-squared test or Fisher's exact test. Kaplan-Meier survival analysis was used to assess 5-year survival in patients with MI and PCI. To compare the survival rate for the entire follow-up period in the two groups, a log-rank test was used. To assess the influence of independent factors on survival and to predict the risk of an event, the Cox regression model was used.

Results

When discharged from the hospital, optimal medication therapy was recommended to all patients. In 1 year only three-quarters of patients continued to take β-blockers and statins, which continued in 5 years of follow-up. The number of patients without anti-thrombotic therapy increased from 19,9% in 12 months to 29,7% in 60 months. The therapy conducted within 60 months didn't result in achieving the target values of lipid profile in any of the groups.

In the course of follow-up, we compared findings dividing the patients into groups with HF-mrEF and HFpEF. During the follow-up, 18 people died (mean age of deceased — 60,9±13,5 years; alive — 60,0±8,9 years). The survival rate in 60 months was 86,7%. Differences in compared groups were not detected (85,0% and 89,1%, respectively, p=0,492).

The blood test data in 12 and 60 months are shown in Table 1. We observed increased values of hs-CRP, MMP-9 and TIMP-1 in both groups of patients, with a downward trend of MMP-9 in the point of 12 and 60 months of follow-up. As for hs-CRP, TNF-α and homocysteine, with a decreasing trend at the second observation point, the trend towards increase at 60 months was recorded. Interleukins had the general trend towards decrease by the 3 observation point as compared to initial data in both groups. Thus, the comparative characteristics of biomarkers in the groups did not differ in the majority of studied parameters. Consistently, the levels of NT-proBNP were higher in the group 1 than in group 2 in 12 and 60 months of follow-up. Moreover, the one-directional changes of NT-proBNP in 12 and 60 months in both groups similar to the dynamics of such inflammatory markers as hs-CRP, TNF-α, homocysteine are notable.

Such laboratory parameters as platelets, homocysteine and increased MMP-9 >249 ng/ml became the independent risk factors of mortality over the follow-up period in the general group of patients. With increase in platelets by $1*10^9$/l, the risk of fatal outcome increases by 1,1%; with increase in homocysteine by 1 μmol/l — by 17,2%; with increase in MMP-9 >249 ng/ml, the risk increases 7 times (Table 2). In 5 years a decrease in the survival rate in patients with a high level of MMP-9 (>249 ng/ml) was recorded. In the 1 group, the death rate was higher among the patients with a platelet count $>245*10^9$/l (Table 3).

Table 3

The impact of laboratory inflammatory markers on the patient survival rate in compared groups

Laboratory parameters	Five-year survival rate	p
Group 1 (HFmrEF)		
MMP-9 >249 ng/ml	75,0%	0,026
MMP-9 <249 ng/ml	96,6%	
Platelets $>245*10^9$/l	74,3%	0,015
Platelets $<245*10^9$/l	93,3%	
Group 2 (HFpEF)		
MMP-9 >249 ng/ml	55,6%	0,000
MMP-9 <249 ng/ml	97,1%	

Abbreviations: MMP-9 — matrix metalloproteinase-9, HFmrEF — heart failure with mid-range ejection fraction.

Discussion

The recorded patterns of changes of vascular inflammatory response parameters and NT-proBNP suggest the need for an association of detected blood changes with a recorded stable decrease in taking medications. We didn't reveal the NT-proBNP effect on survival, however, the meta-analysis of 19 studies showed a prognostic significance of BNP on the relative death risk increase [5]. In both groups of patients, the recorded increased levels of vascular inflammation markers (hs-CRP, MMP-9, TIMP-1, homocysteine, NT-proBNP) suggest the presence of prolonged inflammatory potential for possible cardiovascular event development.

It is considered that increased MMP-9 level is an independent predictor of a cardiovascular event in patients with different types of coronary artery disease, which has a prognostic significance for restenosis development and correlates to a high level of post-infarction LV remodeling due to increased degradation of extracellular matrix proteins and myosin heavy chains, as well as contributes to poor prognosis related to the LV dysfunction [6, 7]. These data are reflected in our research too.

Numerous studies have confirmed that hyperhomocysteinemia is one of the significant and independent risk factors for early and rapid progression of atherosclerosis, endothelial damage, systemic inflammatory response, activation of hemostasis with a poor prognosis in MI patients and is also a predictor of all-cause mortality and cardiovascular events [8, 9]. In our study, this theory was confirmed. The level of homocysteine significantly increased by the 3rd follow-up point in both groups, irrespective of the initial LVEF and was associated with other inflammatory markers and five-year survival in the general group.

In addition to their leading role in atherothrombosis initiation, platelets have important functions in modulating inflammation. They can adhere to intact endothelial cells and promote local vascular inflammation by involving leukocytes through direct interactions or by secreting inflammatory mediators such as chemokines [10]. One of the causes for the increased activity of platelets may be the acceleration of their production and turnover [11]. When thrombocytopoiesis is stimulated, large and reticular "young" platelets appear in the bloodstream, which are not only markers, but also predictors of atherothrombotic events, and, first of all, ACS. An increase in the number of such platelets in patients receiving antiplatelet drugs may be associated with a decrease in the effectiveness of their antiplatelet action [12]. According to our study, an increase in the number of platelets, although to a lesser extent than other biomarkers, affects the mortality rates in patients after MI and PCI during 5-year follow-up, mainly due to patients with HFmrEF, which may be explained by platelet dysfunction due to neurohumoral activation in HF [13].

Thus, today biomarkers are a reliable, safe and objective tool of diagnostics, control of dynamics and risk stratification of adverse events, complementing clinical and instrumental data reflecting the features of the pathophysiological mechanisms of cardiovascular diseases [14]. In general, it should be noted that a multimarker strategy for the management of patients with coronary artery disease and HF may become a promising approach that significantly changes the traditional views on diagnosis and risk stratification.

The key factor for such a biomarker dynamic may lie in the pathogenesis of vascular inflammation course, which depends on the severity of the underlying and comorbid conditions, and on the patients' medical adherence. This multifaceted problem makes it necessary to continue the search for new associations of clinical manifestations and biomarkers in order to reduce the risk of CVDs, including mortality.

Study limitations. During studying the effect of platelet levels on long-term prognosis, we did not study the aggregative activity of platelets, which, undoubtedly, could explain the presented results.

Conclusion

In this study, we identified biomarkers, which make it possible to forecast the risk of 5-year adverse outcomes in patients after MI and PCI. Levels of MMP-9, homocysteine, and platelets were the factors that influenced 5-year survival in the general group of patients after MI and PCI. In the group with HFmrEF, MMP-9 and platelets had a negative impact on the prognosis. In patients with HFpEF, reduced survival was associated only with high levels of MMP-9. The dynamics of markers of systemic inflammatory response and NT-proBNP indicates the prolonged inflammatory process in both groups of patients, persisting for 5 years after MI.

Relationships and Activities: none.

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Concentration of high-sensitivity cardiac troponin I in the oral fluid in patients with acute myocardial infarction: a pilot study

Chaulin A. M.[1,2], Duplyakova P. D.[2], Bikbaeva G. R.[1], Tukhbatova A. A.[1], Grigorieva E. V.[1], Duplyakov D. V.[1,2]

Aim. To assess the potential of using oral fluid as a non-invasive diagnostic material in patients with myocardial infarction (MI).

Material and methods. The pilot, single-center, prospective study included 47 patients with documented MI, among whom there were 33 men (71%) and 14 women (29%) (mean age, 61,72±12,09 years). All patients successfully treated with reperfusion therapy. The control group consisted of 15 people in whom MI was not confirmed. The concentration of high-sensitivity cardiac troponin I (hs-cTnI) in blood and oral fluid was determined using chemiluminescence enzyme immunoassay (CLEIA) on a PATHFAST analyzer (LSI Medience Corporation). Medium sensitivity cardiac troponin I (ms-cTnI) was determined in blood using an Access 2 immunoassay system analyzer (Beckman Coulter, USA). Levels of total bilirubin, creatinine, glucose, rheumatoid factor, alkaline phosphatase and other biochemical parameters were determined on a Furuno CA-400 analyzer (Japan).

Results. The levels of hs-cTnI in patients with MI were significantly higher than in healthy patients both in blood (8,73±1,17 ng/ml vs. 0,012±0,03 ng/ml, p<0,001) and oral fluid (0,41±0,11 ng/ml vs. 0,004±0,001 ng/ml, p<0,001). In patients with AMI, there was a moderate correlation between the concentration of hs-cTnI in the serum and the oral fluid (r=0,319; p<0,05).

The serum level of hs-cTnI in patients with Q-wave (n=33) and non-Q-wave (n=14) MI was 10,11±1,53 ng/ ml vs. 5,48±1,29 ng/ml, respectively (p=0,025). The oral fluid concentration of hs-cTnI in patients with W-wave (n=33) and non-Q-wave (n=14) MI was 0,42±0,14 ng/ml vs. 0,40±0,16 ng/ml, respectively (p=0,925).

The serum level of hs-cTnI in anterior MI (n=19) was 8,92±2,06 ng/ml vs. 8,91±1,81 ng/ml in posterior one (n=23) (p=0,997). The concentration of hs-cTnI in the oral fluid was 0,21±0,06 ng/ml vs. 0,57±0,21 ng/ml, respectively (p=0,107).

The oral fluid concentrations of hs-TnI in patients with MI using conventional plastic tubes (n=26) and special Sarstedt microtubes (n=21) were 0,56±0,19 ng/ml and 0,22±0,10 ng/ml, respectively (p=0,12).

Conclusion. This pilot study has proven the possibility of detecting hs-cTnI in the oral fluid of patients with MI. There was a moderate correlation between the level of hs-cTnI in blood serum and oral fluid. Further research is needed to determine the hs-cTnI reference values in the oral fluid of patients with MI.

Keywords: high-sensitivity cardiac troponin I, myocardial infarction, non-invasive diagnostics, oral fluid.

Relationships and Activities: none.

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Cardiac specific troponins I and T are considered to be the best among all known biomarkers of myocardial damage in terms of sensitivity and specificity [1, 2]. Troponin, whose detection in blood serum was previously considered a key sign of myocardial infarction (MI), can now be regarded as a normal metabolite, since it can be determined even in blood serum of healthy individuals, if a highly sensitive technique is used [2].

Interest in studying the diagnostic potential of oral fluid has been recently shown by specialists in different fields, such as endocrinology, nephrology, dentistry and others [3, 4]. Human saliva is a dynamic biological fluid found mainly in the oral cavity. It is produced mainly by large paired salivary glands (parotid, sublingual, and submandibular), as well as, to a much lesser extent, by minor salivary glands. It is necessary to distinguish saliva from oral fluid. Oral fluid ("mixed saliva") should be considered a mixture of the overall secret of all salivary glands, microorganisms and products of their vital activity, gingival fluid, food residues, etc., while saliva is the secret produced by salivary glands only [4, 5]. The key function of oral fluid is to provide an optimal (satisfactory) environment for the healthy functioning of oral tissues, acting as a buffer lubricant and maintaining the ion reservoir, as well as to assist the normal course of the initial stages of digestion. The property of oral fluid that makes it so valuable to clinicians is that its composition reflects to some extent the levels of biomarkers present in the blood serum that clinicians rely on in diagnosis. Proteomic studies have revealed more than 1 thousand proteins and 19 thousand unique peptide sequences in the oral fluid, many of which have recently been in the focus of studies [3, 6]. The undoubted advantages of oral fluid over blood serum as a biological material can be considered non-invasive, non-traumatic and painless sampling procedure which does not require trained personnel.

Taking into account numerous reports of successful use of oral fluid for the diagnosis of various diseases, we decided to study the diagnostic value of high-sensitive troponin I (hs-TnI) in oral fluid of patients with MI. To address this task, the study was divided into several consecutive stages. At the first stage, which is presented in this article, we planned to investigate the very possibility of detecting elevated levels of hs-TnI in oral fluid of patients with MI.

Thus, the goal of the research was to study the possibilities of using oral fluid as non-invasive diagnostic material in patients with acute MI.

Material and methods

The pilot single-center prospective study was carried out according to the Good Clinical Practice and the principles of the Helsinki Declaration. Patients who participated in the study signed an informed consent form.

The entry criteria were as follows: patients of any gender and age; confirmed MI (time interval of 12 to 24 hours from the moment of hospitalization); myocardial revascularization (percutaneous coronary intervention or thrombolytic therapy); voluntary consent of the patient to participate in the study. Exclusion criteria: chronic kidney disease (CKD) and other pathological conditions that cause a non-coronarogenic increase of cardiac troponins (cardiomyopathies; myocarditis; false-positive interferences of heterophilic antibodies, alkaline phosphatase, bilirubin, rheumatoid factor and other agents).

Venous blood was taken from all the patients by antecubital venipuncture. After that, patients were asked to donate oral fluid by spitting for 1-2 minutes, so that some patients collected oral fluid into ordinary plastic tubes, and others — into Sarstedt micro-tubes (Sarstedt, Germany), specially designed for saliva collection. In this fashion, the diagnostic strength attained with different types of test tubes could be assessed and compared.

Biological material (blood and oral fluid) was delivered to the laboratory for further sample preparation and determination of moderate-sensitive troponin I (ms-TnI) and hs-TnI, as well as a number of biochemical parameters. Blood and oral fluid samples were centrifuged at 3000 rpm for 5 minutes to obtain the supernatant fluid. Some samples of oral fluid (with increased viscosity) were additionally centrifuged to ensure the physical state suitable for analysis.

The determination of Hs-TnI in oral fluid and blood serum was carried out using the PATHFAST rapid compact chemiluminescent immunoassay analyzer (LSI Medience Corporation), and the concentration was expressed in nanograms per milliliter (ng/ml). The principle of the method for the determination of cardiac troponin I is based on chemiluminescent enzyme immunoassay (CLEIA) and consists of several phases: at the first stage, diagnostic antibodies labeled with alkaline phosphatase interact with epitopes of the troponin I molecule; at the second stage, a luminescent substrate is introduced, which is fermented with alkaline phosphatase, which leads to the emission of photons, the intensity of which is detected by a photomultiplier. The signal intensity is directly proportional to the number of diagnostic antibodies bound to the desired antigen (troponin I), and the concentration is calculated from the calibration curve.

Blood serum Ms-TnI was determined using the Access 2 automatic immunoassay analyzer (Beckman

Table 1

Clinical characteristics of groups of examined patients*

Parameter/test	MI patients (n=47)	Control group (n=15)
Age, years	61,72±12,09	57,1±10,2
Sex (male)	33 (71,3%)	7 (46%)
Hypertension (abs.; %)	44 (93,6%)	9 (60,0%)
Prior MI (abs.; %)	10 (21,2%)	2 (13,3%)
Prior cerebrovascular insult (abs.; %)	3 (6,3%)	2 (13,3%)
Peripheral vascular disease (abs.; %)	9 (19,1%)	4 (26,6%)
CHF, FC III-IV (abs.; %)	6 (12,7%)	3 (20,0%)
Smoking (abs.; %)	8 (17,0%)	2 (13,3%)
Diabetes mellitus (abs.; %)	9 (19,1%)	1 (6,6%)
Morphine (abs.; %)	29 (61,7%)	-
Beta-blockers (abs.; %)	47 (100%)	13 (86,6%)
ACE inhibitors (abs.; %)	43 (91,4%)	9 (60%)
Statins (abs.; %)	47 (100%)	9 (60%)
Aspirin (абс.; %)	47 (100%)	9 (60%)
Thrombolytic therapy (abs.; %)	7 (14,8%)	-
Percutanenous coronarography intervention (abs.; %)	40 (85,2%)	-
Increased ms-TnI in blood serum (abs.; %)	47 (100%)	-
Glucose, μmol/L	5,22±0,31	4,62±0,46
Creatinine, μmol/L	109,34±10,82	105,42±9,61
Glomerular filtration rate, mL/min /1,73 m^2	79,11±11,08	83,26±14,15
Rheumatoid factor, IU/mL	5,67±4,56	4,88±3,74
Total bilirubin, μmol/l	12,35±4,57	14,86±3,89
Alkaline phosphatase, U/L	123,48±39,72	118,31±28,01
MI with Q-wave (abs.; %)	33 (70%)	-
MI without Q-wave (абс.; %)	14 (30%)	-
Anterior MI (abs.; %)	19 (40,4%)	-
Posterior MI (абс.; %)	23 (49,0%)	-
MI of unspecified site (abs.; %)	5 (10,6%)	-

Note: * — no significant inter-group differences in any parameter.
Abbreviations: ACE — angiotensin-converting enzyme, MI — myocardial infarction, FC — functional class, CHF — chronic heart failure.

Table 2

Concentration of hs-TnI in patients with acute MI and in control group

	MI patients (n=47)	Control group (n=15)	P
hs-TnI, ng/mL (in blood serum)	8,73±1,17	0,012±0,03	p<0,001
hs-TnI, ng/mL (in oral fluid)	0,41±0,11	0,004±0,001	p<0,001

Note: M — arithmetic mean value, m — arithmetic mean error, p — significance level attained.
Abbreviations: hs-TnI — high-sensitive troponin I, MI — myocardial infarction.

Coulter, USA). Biochemical parameters (glucose, creatinine, rheumatoid factor, alkaline phosphatase, total bilirubin) were measured using the Furuno CA-400 automatic analyzer (Japan).

The obtained data were analyzed using the Statistica 7.0 package. The results were expressed as M±m (arithmetic mean and arithmetic mean error, respectively). Case-control groups were compared using unpaired and independent Student t-tests. Relationships (correlations) were studied using Pearson correlation analysis. The critical significance level, p, was chosen to be 0,05.

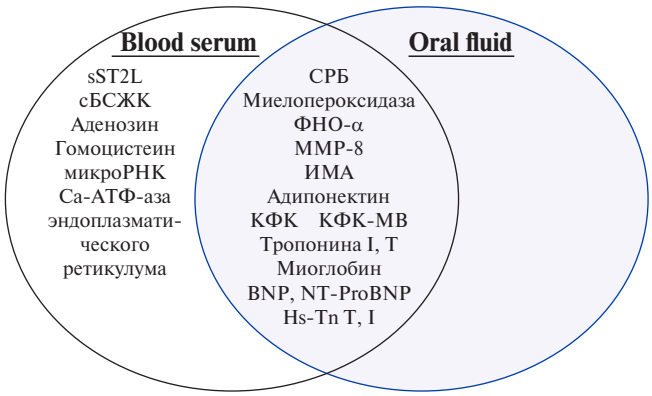

Figure 1. Basic cardiac biomarkers found in blood serum and oral fluid [2].
Abbreviations: ATP — adenosine triphosphate, IMA — ischemia modified albumin, CPK — creatine phosphokinase, CPK-MB — creatine phosphokinase-MB, CRP — C-reactive protein, CVD — cardiovascular disease, h-fabp — heart-type fatty acid binding protein, TNF-α — tumor necrosis factor α, MMP-8 — matrix metalloproteinase-8, BNP — brain natriuretic peptide, NT-proBNP — N-terminal pro B-type natriuretic peptide, sST2L — isoform of ST2 protein, Hs-Tn — high-sensitive troponin.

Results

The study included 62 patients. The main group included those with confirmed MI diagnosis (n=47), and the control group consisted of patients (n=15) hospitalized with other diseases (prior MI, stable angina pectoris, chronic heart failure, cardiac arrhythmias, hypertension). The clinical profile of the patients is presented in Table 1.

Patients of the main and control groups did not differ in age significantly, but men predominated among patients of the main group (71,3%). Creatinine levels and estimated glomerular filtration rate did not differ significantly between the groups. The absence of an increase in the level of a number of biochemical parameters (rheumatoid factor, total bilirubin, alkaline phosphatase) allowed us to practically exclude false-positive interference. In general, the levels of biochemical parameters (glucose, creatinine, rheumatoid factor, total bilirubin and alkaline phosphatase) did not differ significantly between the groups.

Myocardial revascularization was performed in all patients. MI with Q-wave was formed in 70% of patients, and 30% were without Q-wave.

In all 47 patients of the main group, ms-TnI level was higher than the upper reference limit (>0,4 ng/mL), while in the control group it was not detected (0,00 ng/mL) or its values were below 0,02 ng/mL.

Serum hs-TnI level in MI patients was also many times higher than the threshold value (99th percentile is >0,015 ng/mL for our test system; to convert to common measurement units, ng/L must be multiplied by 1000, which gives 15 ng/L) and amounted to 8,73±1,17 ng/mL. In patients of the control group (n=15), the serum hs-TnI concentration was 0,012±0,03 ng/mL, the significance level for intergroup differences being p<0,001.

The oral fluid of patients with confirmed MI showed significantly higher hs-TnI level compared to that in the control group: 0,41±0,11 ng/mL vs. 0,004±0,001 ng/mL (p<0,001) (Table 2). A moderate correlation was found between the concentration of hs-TnI in blood serum and oral fluid in patients with MI (r=0,319; p<0,05).

Serum levels of hs-TnI in patients with MI with Q-wave (n=33) and without it (n=14) were 10,11±1,53 ng/mL vs. 5,48±1,29 ng/mL, respectively (p=0,025). Concentrations of hs-TnI in the oral fluid in patients with MI with Q-wave (n=33) and without Q-wave (n=14) were 0,42±0,14 ng/mL vs. 0,40±0,16 ng/mL, respectively (p=0,925).

The level of hs-TnI in blood serum in patients with the anterior MI (n=19) was 8,92±2,06 ng/mL vs. 8,91±1,81 ng/mL for the posterior MI (n=23) (p=0,997). The concentration of hs-TnI in the oral fluid is 0,21±0,06 ng/mL vs. 0,57±0,21 ng/mL for the anterior and posterior MI, respectively (p=0,107).

Concentrations of hs-TnI in the oral fluid of MI patients using conventional plastic tubes (n=26) and special Sarstedt micro-tubes (n=21) were 0,56±0,19 ng/mL and 0,22±0,10 ng/mL, respectively (p=0,12).

Discussion

To date, most of the biomarkers of cardiovascular diseases present in blood have also been identified in oral fluid (Figure 1) [2]. However, the number of studies devoted to the non-invasive determination of cardiac biomarkers is still relatively small; therefore, further research is needed.

Our findings of an increase in the level of hs-TnI in the oral fluid of MI patients are consistent with studies by other authors [7-10]. A group of American researchers headed by Floriano PN (2009) was the first to identify >20 biomarkers, including troponin I, in the oral fluid of MI patients using the lab-on-a-chip nanotechnology (LOC) [7]. Subsequently, Miller CS et al. (2010) found elevated levels of myoglobin in the oral fluid of MI patients [8]. Mirzaii-Dizgah I et al. (2013) conducted a number of studies in which biomarkers of MI (creatine kinase MB-fraction and cardiac troponins T and I) were determined in the oral fluid of patients using enzyme-linked immunosorbent assay [9, 10].

However, the currently available results are not sufficient for using in clinical practice. First of all, it should be noted that there are no specific reference values for the levels of cardiac troponins

in other biological fluids, particularly in oral fluid, due to the relatively small number of studies [2]. Troponin levels measured in oral fluid are different in different researchers. The obvious discrepancy in concentrations obtained in different studies can be explained by the use of different commercial setups and methods for the determination of concentrations of troponins. Diagnostic antibodies that are part of immunoassays differ in that they are aimed at different antigenic determinants of the molecules of troponins. In other words, different test systems for the determination of troponins detect different epitopes of molecules of the heterogeneous troponin fraction: free troponin molecules, troponin complexes, troponin fragments of different sizes and molecular weight, as well as their oxidized and phosphorylated derivatives [2]. In the present study, a highly sensitive chemiluminescence enzyme immunoassay was used, in contrast to the studies by Floriano PN (2009) and Mirzaii-Dizgah I (2013), where LOC and enzyme-linked immunosorbent assay were used [7, 9, 10].

In the present study, it was found that the serum level of hs-TnI in MI patients with Q-wave was significantly higher than that in MI patients without Q-wave (p=0,025), but the respective differences in oral fluid were not statistically significant. The localization of ischemic damage did not substantially affect the result: there were no significant differences of either serum or salivary levels of hs-TnI between patients with anterior and posterior infarction. It is very likely that this is due to the phenomenon of leaching of troponins from the necrotic zone, which is determined by the degree of reperfusion, as well as by many other parameters, such as the time of admission of patient and the time of sampling of biological material, method used for the determination of troponins, and others. Thus, according to the study by Chia S. et al., the best correlation of troponin level with the size of infarction was observed 72-96 hours after the onset of ischemic symptoms for patients who underwent percutaneous coronary intervention [11]. In our study, however, the biological material was taken 12-24 hours after the admission of patients. In addition, we found no significant differences in the measured levels of hs-TnI in the oral fluid of patients when different test tubes were used for sampling.

Human biological fluids, including oral fluid, are considered ultrafiltrates of blood plasma, and therefore contain almost the same components, but in different ratios, which is primarily due to the mechanisms of their transport (filtration) [2, 10, 12]. Mechanisms of transport of troponins to other biological fluids through blood-tissue barriers are debatable. So, for example, according to some researchers, troponins are too large protein molecules to pass through the glomerular and blood-saliva filters (barriers). Indeed, in Ziebig R, et al. (2003), in most MI patients, troponin I was not detected in urine, and the authors concluded that cardiac troponins, due to their size, cannot pass through the glomerular filter [12, 13]. At the same time, patients with CKD may have elevated levels of troponins even in the absence of coronary pathology. Moreover, in patients with more severe CKD (more pronounced inhibition of glomerular filtration), troponin levels were higher than in patients with initial stages of CKD, and therefore a number of researchers give the kidneys a leading role in the elimination of troponins from the blood [12]. In addition, a recent study found troponin I in the morning urine of all healthy patients as well as patients with high blood pressure; moreover, troponin I concentrations in patients with hypertension were significantly higher than in normotonic patients. This can be considered the direct evidence of the role of kidneys in the elimination of troponins. Probably the success of this study [14] can be ascribed to the use of highly sensitive immunoassay, in contrast with the study by Ziebig R [13], who used a moderately sensitive system, whose detection ability was not enough to detect such relatively low concentrations of troponin I.

One of the factors contributing to the filtration of troponins through narrow pores is intra- and extracellular degradation into smaller fragments. According to current data, several tens of fragments of various sizes and molecular weights are found in blood serum. Apparently, smaller fragments can penetrate the blood-tissue interface, as evidenced by numerous studies in which troponins were found in urine [14], cerebrospinal fluid [15] and oral fluid [2, 7, 9, 10]. These fragments are though “visible” only to those test systems that contain antibodies specific to them.

Another important factor affecting the diagnostic strength of all laboratory tests such as oral fluid studies is the preanalytical stage, which largely depends on how accurately all recommendations regulating the sampling of biological material and the work of health care personnel are followed. According to current data, the most frequent errors related to incorrect test results are caused by preanalytical mistakes in 70% of cases. The preanalytical stage, including the sampling conditions and the details of sample preparation, is also not standardized and is different in different researchers, and this could of course have affected the results.

Among the limitations of this method for the determination of troponin I are that the result can be influenced by the state of the oral mucosa and concomitant (background) dental diseases, the time

of eating, the mode of teeth brushing and rinsing the oral cavity, saliva collection speed. In our future studies, we are planning to take these points into account to improve the effectiveness of the use of oral fluid for the diagnosis of MI.

Conclusions

The present pilot study has proved that it is possible to detect hs-TnI in the oral fluid of patients with confirmed MI. There is a moderate correlation between the levels of hs-ThI in the blood serum and oral fluid, which may be due to the characteristics of the preanalytical stage or the state of the oral mucosa. Further studies are needed to determine the reference values for the hs-ThI content in the oral fluid in MI.

Relationships and Activities: none.

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Prognostic significance of a combination of novel biomarkers in the long-term stratification of adverse outcomes in patients with ST-segment elevation myocardial infarction

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A multi-marker approach for assessing the prognosis of patients with ST-segment elevation myocardial infarction (STEMI) is a promising strategy.

Aim. To assess the potential prognostic power of soluble growth stimulation gene-2 (sST2), pentraxin 3 (Ptx-3), and N-terminal pro-brain natriuretic peptide (NT-proBNP) in stratification of the risk of major cardiovascular events (CVE) during 2-year follow-up after STEMI.

Material and methods. In 154 patients with STEMI, serum concentrations of NT-proBNP, sST2, and Ptx-3 were determined upon admission to hospital. During the two-year follow-up period (734,2±61,2 days), correlation of biomarker concentrations with the risk of a composite endpoint (myocardial infarction + stroke + hospitalization due to cardiovascular disease + cardiovascular death) was analyzed.

Results. In the 2-year follow-up, CVE were observed in 81 (55,1%) patients (CV death (n=33; 22,1%), recurrent MI (n=28; 18,8%), stroke (n=8; 5,4%), hospitalization due to cardiovascular disease other than MI, stroke or cardiovascular death (n=12; 8,2%)). NT-proBNP (HR, 1,19; 95% CI, 1,018-1,32, p<0,001) and sST2 (HR, 1,000013; 95% CI, 1,00-1,001, p=0,007) correlated with CVE in contrast to Ptx-3 (HR, 1,178; 95% CI, 0,798-1,73, p=0,434). The most accurate prediction of CVE was shown in the model with three biomarkers (AIC=831, BIC=843, LR=12,45, p=0,033).

Conclusion. After STEMI, NT-proBNP and sST2, but not Ptx-3, predicted CVE, while 3-marker analysis showed higher accuracy compared to single- and double-marker.

Keywords: STEMI, cardiovascular events, cardiovascular death, risk stratification, sST2, NT-proBNP, pentraxin-3.

Relationships and Activities: none.

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Despite the development of new therapeutic strategies, coronary artery disease remains one of the prioritized healthcare problems all across the globe. ST-segment elevation myocardial infarction (STEMI) leads to both long-term complications and unfavorable cardiovascular diseases (CVDs) over a long period [1]. Thus, one of the most important goals in routine clinical practice is to identify such patients from the risk group.

Using cardiospecific markers facilitates improvement in diagnostics and allows for complication risk stratification and CVD monitoring both during hospitalization and over a long (1-5 years) period [2]. Their concentration correlates with the severity of a cardiovascular event, shows the dynamic of disease and the efficiency of ongoing therapy. Alongside traditionally used biomarkers such as creatine-phosphokinase MB, aspartate aminotransferase, and now commonly used in clinical practice troponins T and I, "new" serum biomarkers rise to popularity: a soluble form of a stimulating growth factor (sST2), pentraxin 3 (Ptx-3), N-terminal pro-brain natriuretic peptide (NT-proBNP). Their concentration allows for the identification of different damage mechanisms affecting myocardial tissues [3, 4]. Indeed, high levels of NT-proBNP are prognostically important for the evaluation of sudden death risks, repeated MI, and chronic heart failure (CHF) not only in patients with MI but also in patients with unstable angina [4]. Nevertheless, the sensitivity and specificity of such markers remain low [5]. Thus, we need additional instruments for cardiovascular outcomes evaluation.

It is proven that multimarker analytical approaches increase the sensitivity and specificity of a prognosis. Therefore, they can be a more efficient instrument for estimating unfavorable CVDs in patients with MI. "New" serum biomarkers such as sST2 and Ptx-3 have been recently presented as a potentially efficient instrument for CVD risks stratification improvement [6]. Ptx-3 is related to the family of pentraxins, while sST2 is a member of the interleukin-1 receptor family and a stimulating growth factor. An increase in its concentration in the blood indicates a higher risk of unfavorable outcomes for patients with MI and heart failure [7]. A Ptx-3 increase is common in patients with coronary artery disease including acute coronary syndrome (ACS) while its high concentration in plasma is a predictor of negative clinical outcomes in patients with HF both with reduced and preserved ejection fraction (EF) [8]. Nevertheless, the prognostic ability of both biomarkers to evaluate outcomes in patients surviving MI remains a highly debated topic. While Ptx-3 levels in blood plasma predict clinical outcomes in patients with HF, its prognostic ability for patients with MI in the long run is still unclear. In our previous studies, we discovered that in patients with STEMI high presence of sST2, Ptx-3, and NT-proBNP were associated with mortality from cardiovascular diseases while the multimarker approach improved the stratification accuracy of this endpoint [9]. Whether a combination of "new" biomarkers such as NT-proBNP, sST2, and Ptx-3 in patients with STEMI can improve the long-term prognostic accuracy for the composite endpoint, remains unclear.

The aim was to evaluate the potential of stratification of the composite endpoint in patients with STEMI using a combination of serum biomarkers NT-proBNP, sST2, and Ptx-3. Throughout the 2-year follow-up period, we determined the interrelation between initial concentrations of biomarkers in the blood serum and the prevalence of unfavorable cardiovascular events such as MI, stroke, cardiovascular-related hospitalizations, and deaths.

Material and methods

In this prospective randomized single-center study we included 154 patients hospitalized due to STEMI to the vascular center. The diagnosis was produced using data from electrocardiography (ECG) and verified clinically using follow-up ECG, echocardiography, coronary angiography, and laboratory results according to guidelines of the European Society of Cardiology (ESC) [10].

Depending on the timeframe of symptoms manifestation and availability of coronary angiography, patients were treated with immediate coronary angiography or thrombolysis. Thrombolysis before admission was due to a fraction of patients from remote regions requiring more time to be delivered to the hospital. Thrombolytic therapy only was used for patients who declined coronary angiography or had nephropathy (13 patients out of 147). In cases of inefficient thrombolytic therapy, coronary angiography was performed as soon as possible (Table 1). During coronary angiography, stenting of the infarct-related artery was performed for all 134 patients. Drug therapy and recommendations for further treatment following an MI were conducted according to ESC guidelines [10].

This study is the continuation of our previous study published in January 2020 in the Journal of Clinical Medicine [9] for the same cohort of patients. It contained an analysis of the predictive abilities of the biomarker in relation to cardiovascular mortality.

The study was conducted in accordance with Good Clinical Practice standards and principles of the Declaration of Helsinki. The protocol was approved by

the Local Ethics Committee. Before the inclusion, all participants provided a written informed agreement.

There were following inclusion criteria: age over 18 years and STEMI in accordance with ESC guidelines. Exclusion criteria were as follows: over 48 hours after the ACS onset, severe valvular dysfunction such as severe regurgitation or stenosis, dilated cardiomyopathy, severe atrial fibrillation and/or atrial flutter, second- and third-degree atrioventricular block based on anamnesis or ECG, implanted cardiac pacemaker, acute pulmonary embolism, and recent (<3 years) severe disease, chronic obstructive pulmonary disease or bronchitis; acute infectious diseases at admission, renal failure with glomerular filtration rate less than 30 ml/min/1,72m^2, pregnancy and lactation.

The design of the study is presented in Figure 1. During the first 3 hours after the arrival, venous blood from patients was collected, centrifuged, and the serum was frozen for further analysis. The concentration of NT-proBNP, sST2, and Ptx-3 was analyzed using enzyme-linked immunosorbent assay (Critical diagnostics, USA, Biomedica, Slovakia, Hycult Biotech, USA). Follow-up analysis was conducted after 2 years ± 3 months (734,2±61,2 days) from STEMI using the regional informational analytical system PROMED. This program allows to remotely monitor releases from hospitals and death certificates. In cases when no such entries existed, patients were contacted via telephone to prevent data loss.

The composite endpoint (negative cardiovascular events) was determined as the frequency of repeated MI + stroke + cardiovascular-related hospitalizations + cardiovascular mortality during the follow-up period. Patients who died within the first 6 days of the initial hospitalization, patients died from other reasons (trauma, cancer, suicide, etc.), and patients with whom contact was lost were excluded from the analysis. There were 9 such patients: 2 died due to traumas, 1 patient died from cancer, and 2 patients died within 5 days after hospitalization. Also, contact was lost with 4 other patients due to moving. These patients were also excluded from the analysis.

The statistical analysis was conducted using SPSS 21 and R Studio software. Data are presented as median values (M) and standard deviation. The Mann-Whitney test were used to determine differences between subgroups since it has the highest statistical power among non-parametric tests for small sample pools. Qualitative traits were analyzed using standard statistical chi-squared test. To evaluate the prognostic value of parameters, the area under the ROC curve (AUC) was determined while threshold values were also calculated using ROC curves. The differences were considered significant at p<0,05. The statistical processing was conducted using SPSS 2 and MedCalc 8.2.0.3 software.

Table 1

Parameters of the studied group

Parameter	Value
N	147
Sex (Male), n (%)	118 (80,3)
Age, years	60,9±12,1
LVEF (%)	52,8±7,2
Stroke, n (%)	5 (3,4)
Prior MI, n (%)	34 (23,1)
CABG, n (%)	1 (2,9)
Coronary angiography and artery stenting, n (%)	15 (44,1)
Smoking, n (%)	86 (58,5)
Hypertension, n (%)	138 (93,9)
Type II diabetes, n (%)	23 (15,6)
Revascularization strategy	
Immediate TLT, n (%)	13 (8,8)
Immediate TLT with following CAG, n (%)	22 (15,0)
Immediate CA, n (%)	112 (76,2)
Affected arteries during CAG: LCA, n (%) AIA, n (%) CA, n (%) RCA, n (%) Multiple lesion, n (%)	 1 (0,7) 51 (38,1) 12 (8,9) 48 (35,8) 12 (8,9)
Therapy after release	
ACE inhibitors/sartans, n (%)	143 (97,3)
B-blockers, n (%)	139 (94,6)
Diuretics, n (%)	51 (34,7)
Aldosterone antagonists, n (%)	37 (25,2)
Ivabradine, n (%)	12 (8,1)
Statins, n (%)	139 (94,6)
Acetylsalicylic acid, n (%)	142 (96,0)
Thienopyridine, n (%) — Clopidogrel, n (%) — Ticagrelor, n (%)	138 (93,8) 110 (78,7) 28 (21,3)
DOAC and Warfarin, n (%)	7 (4,8)

Abbreviations: CABG — coronary artery bypass grafting, ACE — angiotensin-converting-enzyme, MI — myocardial infarction, LCA — left coronary artery, DOAC — direct oral anticoagulants, RCA — right coronary artery, AIA — anterior interventricular artery, LVEF — left ventricular ejection fraction, TLT — thrombolytic therapy.

Results

Table 1 contains parameters of the studied cohort as well as examinations and treatments during the hospitalization period and recommendations given upon release from the hospital. Men (n=118) prevailed over women (n=29). Among comorbidities,

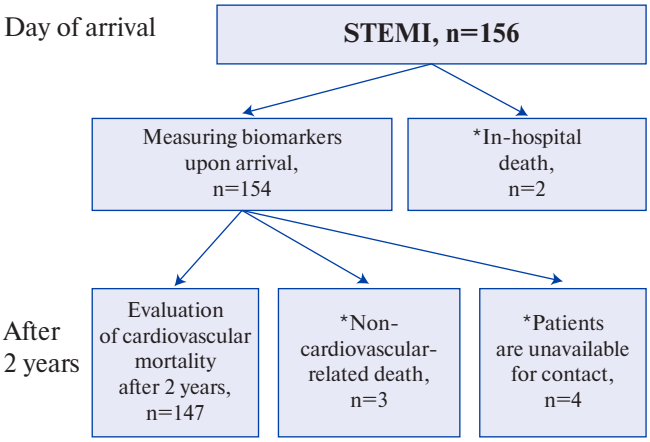

Figure 1. Study design.
Note: * — patients were excluded from the study.
Abbreviations: STEMI — ST-elevation myocardial infarction, CV — cardiovascular.

Table 2
Biomarker parameters in the general group

Parameter	Value	Reference value
n	147	
Creatinine, mmol/l	100,97±25,28	male — 80-115, female — 53-97
CPK-MB, mmol/l	112,16±94,47	5-24
Troponin I, ng/ml	1625,4±2882,1	0-0,1
NT-proBNP, pg/ml	1342,8±1648,2	0,5-30
sST2, ng/ml	58,17±60,03	male — 8,5-49,3, female — 7,1-33,5
Ptx-3, ng/ml	170,9±117,29	-

Abbreviations: CPK-MB — creatine phosphokinase-MB, NT-proBNP — N-terminal pro-brain natriuretic peptide.

Table 3
Cardiovascular events in the group after 2 years

	STEMI, n=147
Deceased, n	33 (22,1%)
MI, n	28 (18,8%)
Stroke, n	8 (5,4%)
Hospitalization, n	12 (8,2%)
Composite endpoint (CVE)	81 (55,1%)

Abbreviations: MI — repeated myocardial infarction, STEMI — ST-segment elevation myocardial infarction, CVE — cardiovascular events.

hypertension (n=167, 92%), prior MI (42,23%), type II diabetes (31,17%) were observed. Drug therapy during and after hospitalization was in accordance with current ESC guidelines [10].

During statistical analysis, we obtained median values for relevant biomarkers. These results are presented in Table 2. For the time being, normative values for Ptx-3 are not established. All values in patients with ACS from the general group were increased several folds, especially troponin I.

Over 2 years (734,2±61,2 days), the composite endpoint for cardiovascular events (MI + stroke + cardiovascular-related hospitalizations + cardiovascular mortality during) was observed in 81 patients (55,1%: cardiovascular mortality, 33 (22,1%), repeated MI, 28 (18,8%), stroke, 8 (5,4%), cardiovascular-related hospitalizations, 12 (8,2%)) (Table 3).

The statistical analysis was conducted using the described mathematical model. Two years after a STEMI, ROC-analysis was used to evaluate cut-off points of studied biomarkers depending on cardiovascular events (Table 4, Figure 2). The logarithmic criterion and Gehan-Wilcoxon test showed a reliable cardiovascular events biomarker cut-off point only for NT-proBNP (>2247 pg/ml, p=0,02) (Table 5).

Kaplan-Meier survival curves were created for cardiovascular events frequency after 2 years above and below cut-off points for biomarkers NT-proBNP, sST2, and Ptx-3 (Figure 3). We observed a slight divergence in survival between cardiovascular events frequency for NT-proBNP and sST2 while Ptx-3 curves were nearly identical.

During the next stage, endpoints of biomarkers were analyzed using the Cox regression. NT-proBNP and Ptx-3 values were presented in logarithmic form and sST2 — in quadratic. Table 4 presents Cox regression coefficients for cardiovascular events for studied biomarkers. To evaluate mortality coefficients in the Cox model, we used the Efron approximation (partial likelihood). Indeed, in Cox regression, biomarkers NT-proBNP and sST2 were able to predict cardiovascular events (p<0,01). The NT-proBNP (AUC=0,8, p<0,001) demonstrated a higher prognostic value for cardiovascular events compared to sST2 (AUC=0,625, p=0,02).

Using Gehan-Wilcoxon tests and logarithmic analysis, parameters of patients (Table 1 and 2) were analyzed to evaluate control variables associated with cardiovascular events throughout the follow-up period (p<0,1). It was discovered that the following parameters were associated with cardiovascular events with p<0,1: NT-proBNP, sST2, Ptx-3, age over 5 years, male sex, and a high level of troponin I. Biomarkers NT-proBNP, sST2, and Ptx-3 were binarized and transformed into fictitious variables according to cut-off points obtained above using ROC analysis. It was done to analyze the combined effect of risk factors (RF) on cardiovascular

Table 4

Cut-off points for biomarkers for CVE over the 2 years after STEMI

Biomarker	CVE				
	Cut-off point	Sensitivity, %	Specificity, %	AUC	p
NT-proBNP, pg/ml	>2247	38,8	85,7	0,625	0,020
sST2, ng/ml	>110	68,2	50,0	0,477	0,814
Ptx-3, ng/ml	>122,0	72,5	44,3	0,526	0,593

Abbreviations: NT-proBNP — N-terminal pro-brain natriuretic peptide, sST2 — soluble suppression of tumorigenicity 2, Ptx-3 — pentraxin 3, CVE — cardiovascular events.

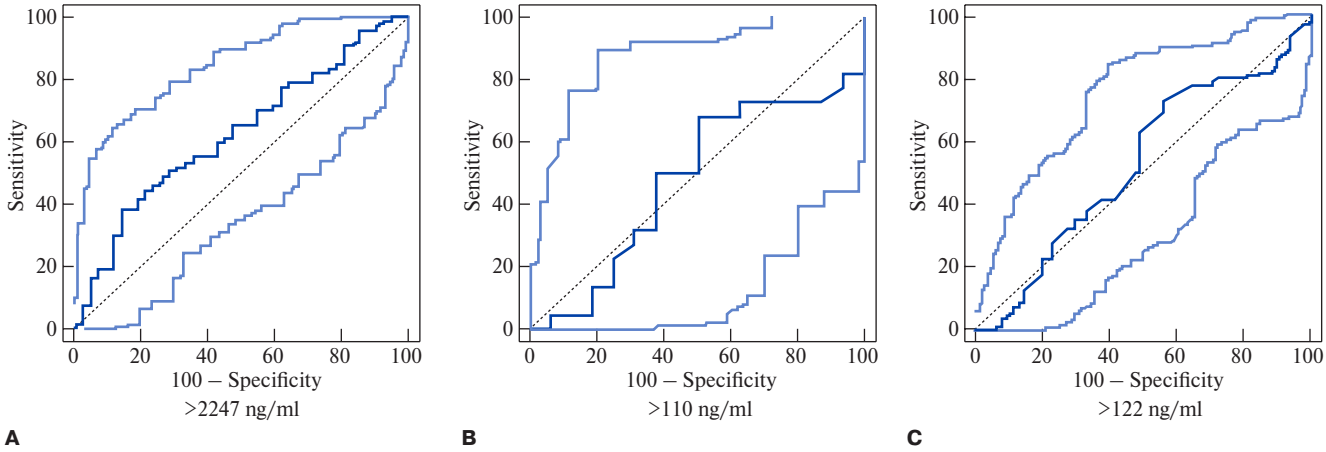

Figure 2. ROC analysis of cut-off points for cardiovascular events for NT-proBNP (**A**), sST2 (**B**), and Ptx-3 (**C**) after a 2-year follow-up period after STEMI.

Table 5

Cox regression for biomarkers and CVE prevalence after STEMI

Biomarker	Coefficient±SD	Hazard ratio	AUC	95% CI	P
Log (NT-proBNP)	0,1781±0,051	1,19	0,526	1,08-1,32	0,0006
sST2^2	a,000013±0,000000007	1,000013	0,625	1,00-1,001	0,007
Log (Ptx-3)	0,167±0,20	1,178	0,477	0,798-1,73	0,4344

Abbreviations: CI — confidence interval, NT-proBNP — N-terminal pro-brain natriuretic peptide.

events throughout the 2-year follow-up period with a comparatively small volume of initial data. Additionally, discrete variables allow for a more accurate interpretation of the risk ratio in the Cox model.

During the next stage, we conducted a comparison of prognostic power between multimarker approaches (various combinations of NT-proBNP, sST2, and Ptx-3) for cardiovascular events based on information criteria Akaike (AIC) and Schwartz (BIC) with control variables. Variables of NT-proBNP, sST2, and Ptx-3 biomarkers were transformed into binary form for both models. The comparison between two biomarker models (sST2 + NT-proBNP, sST2 + Ptx-3, and NT-proBNP + Ptx-3) and the model with three biomarkers allowed us to find the most accurate variant according to AIC and BIC statistical parameters. Table 5 presents the results for coefficients and multifactor analysis of risks in the Cox model for cardiovascular events over the 2-year follow-up analysis. The most accurate prognosis was found for the model with three biomarkers although with a low likelihood ratio (LR) of 12,45 (p=0,034). It should be noted that the combination of NT-proBNP and sST2 was only slightly behind the three-component cut-off point with LR 12,44 (p=0,034, Table 6).

Discussion

For rational risk stratification in patients with STEMI and to acquire additional prognostic information, it was suggested to use a combination of serum biomarkers involved in a variety of pathological reactions associated with cardiovascular

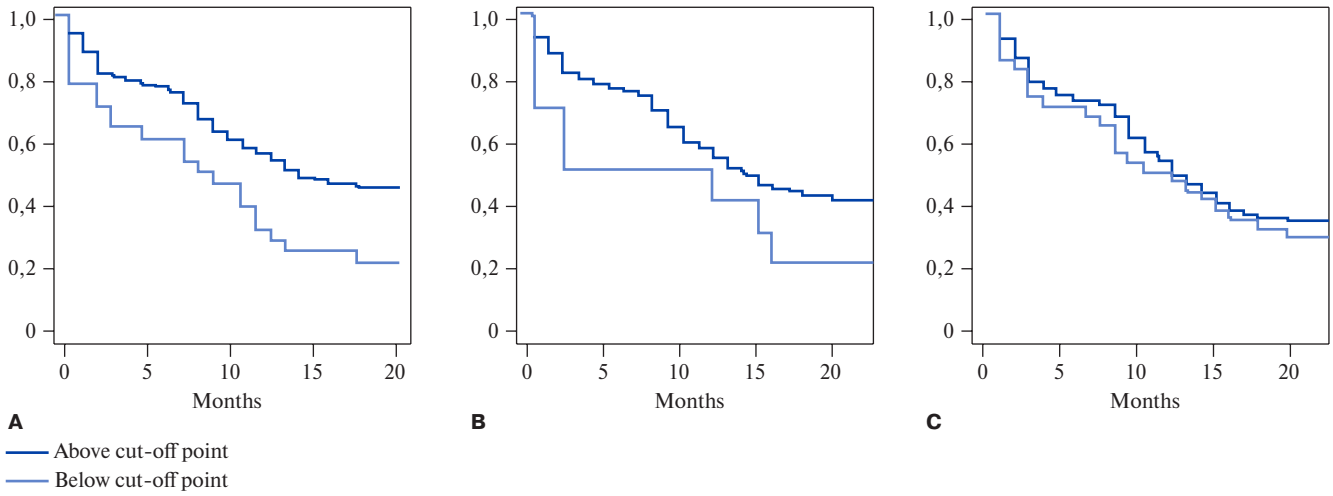

Figure 3. Kaplan-Meier survival curves for cardiovascular events during a 2-year analysis for NT-proBNP (**A**), sST2 (**B**), and Ptx-3 (**C**).

Table 6

Multivariable regression analysis of RF for different combinations of biomarkers 2 years after STEMI

Biomarker and cut-off values	Coefficient±SD	HR	95% CI	p
Combination NT-proBNP + sST2 + Ptx-3 (AIC=831, BIC=843, LR=12,45, p=0,033)				
NT-proBNP >2247 pg/ml	0,54±0,26	1,72	1,03-2,86	0,037
sST2 >110 ng/ml	-0,04±0,33	0,96	0,51-1,82	0,902
Ptx-3 >122 ng/ml	0,31±0,24	1,37	0,85-2,20	0,199
Age >65 years	0,31±0,24	1,17	0,84-2,21	0,219
Male	0,121±0,22	1,13	0,72-1,74	0,599
Troponin I	0,35±0,21	1,42	1,15-1,75	0,174
Combination NT-proBNP + Ptx-3 (AIC=828, BIC=838, LR=10,76, p=0,034)				
NT-proBNP >2247 pg/ml	0,54±0,26	1,72	1,03-2,86	0,037
Ptx-3 >122 ng/ml	0,31±0,24	1,36	0,86-2,15	0,196
Age >65 years	0,31±0,24	1,36	0,84-2,21	0,214
Male	0,111±0,21	1,12	0,91-1,38	0,606
Troponin I	0,37±0,20	1,45	1,19-1,77	0,160
Combination NT-proBNP + sST2 (AIC=830, BIC=840, LR=12,44, p=0,034)				
NT-proBNP >2247 pg/ml	0,58±0,26	1,78	1,07-2,96	0,023
sST2 >110 ng/ml	0,08±0,32	1,08	0,58-2,04	0,805
Age >65 years	0,33±0,25	1,39	0,85-2,26	0,185
Male	0,15±0,23	1,16	0,92-1,46	0,521
Troponin I	0,41±0,21	1,51	1,22-1,86	0,091
Combination sST2 + Ptx-3 (AIC=833, BIC=843, LR=8,27, p=0,081)				
sST2 >110 ng/ml	-0,048±0,32	1,72	0,50-1,79	0,881
Ptx-3 >122 ng/ml	0,36±0,24	1,43	0,89-2,29	0,137
Age >65 years	0,48±0,23	1,61	1,04-2,52	0,034
Male	0,15±0,22	1,13	0,72-1,74	0,599
Troponin I	0,40±0,21	1,49	1,20-1,84	0,101

Abbreviations: CI — confidence interval, HR — hazard ratio, LR — likelihood ratio, NT-proBNP — N-terminal pro-brain natriuretic peptide.

events [11]. The majority of multimarker approaches include an addition of new promising biomarkers to the pool of well-studied RFs [12, 13]. Patients with high-risk experience longer hospitalization, higher hospitalization rate, higher frequency of ICD implantations, and thus they are recommended a different strategy of secondary prophylaxis, rehabilitation, etc.

Alongside standard biomarkers, the prognostic value of "new" biomarkers NT-proBNP (myocardial stress marker), sST2 (myocardial fibrosis and remodeling marker), and Ptx-3 (inflammation marker) was analyzed in 147 patients with STEMI in terms of negative cardiovascular events (after 2 years. In this study, for the cardiovascular endpoint, the sST2 cut-off point was >47 ng/ml (hazard ratio (HR), 1,000012, 95% confidence interval (CI), 1,000-1,001, p=0,071, 68,2%, 50,7%), NT-proBNP >463,0 (HR, 1,19, 95% CI 1,018-1,32, p<0,01, 38,8%, 85,7%). Kaplan-Meier survival curves above and below the cut-off point revealed a divergence between curves for NT-proBNP and sST2, but not for Ptx-3.

In the Bayes-Genis A, et al. (2015) study, in 1015 patients with HF with reduced EF, sST2 showed long-term risk stratification in patients with different concentrations of biomarkers of other pathogenetic classes in the blood serum [10]. Hence, the death risk ratio based on the sST2 was 1,22 (95% CI, 1,08-1,37; p=1,001) in the upper tercile of NT-proBNP and 2,02 (95% CI, 1,61-2,52; p=1,001) in the lower tercile of NT-proBNP. A multicenter study with 1141 outpatients with systolic heart failure revealed that the risk of cardiovascular endpoints was higher when the concentration of sST2 was ⩾36,3 ng/ml compared to when it was sST2 <22,3 ng/ml (HR, 1,9; 95% CI, 1,3-2,9; p=0,002) [12]. This fact suggests that sST2 on its own cannot be considered an RF which was confirmed in the CLARITY-TIMI study [4]. Ehab K, et al. (2016) determined the level of serum Ptx-3 in STEMI patients. In patients with STEMI, the level of Ptx-3 was significantly higher compared to the control group and it was recommended to use it as an early MI marker [13]. The cut-off point was 4,35 ng/ml, also lower than in our study. As pointed out above, during MI, the low specificity of sST2 in relation to endpoints can be observed [4]. However, the prognostic ability was high for the combination of sST2 and NT-proBNP. It increased from 0,82 (95% CI, 0,77-0,87) to 0,86 (95% CI, 0,81-0,90; p=0,017). The combination of sST2 and NT-proBNP significantly improved the risk stratification accuracy. High levels of Ptx-3 predicted long-term mortality in several prospective observational studies [14, 15]. In our previous studies, the significance of biomarker combination (sST2 + Ptx-3 + NT-proBNP) in patients with STEMI for cardiovascular mortality diagnosis was already demonstrated [9, 16]. In another, similar in terms of design with ours, study, AUC was 0,872 for sST2 (sensitivity, 76,27%; specificity, 85,92%) and 0,902 for NT-proBNP (96,61%, 77,69%) while levels of sST2 in serum and NT-proBNP were independent RF for cardiovascular events [17]. In 1401 patients with STEMI, the median sST2 was 48,7 ng/ml and higher values were associated with higher excessive mortality risk and heart failure independent from other prognostic parameters over the course of 5-year follow-up [7].

In this study, in 147 patients with STEMI throughout 2-year follow-up analysis, we studied the ability of serum biomarkers sST2, Ptx-3, and NT-proBNP to stratify risks of unfavorable cardiovascular events. Two years after MI, NT-proBNP and sST2 separately predicted cardiovascular events while the two-marker combination of NT-proBNP and sST2 was significant in cardiovascular events prognosis (LR=12,44, p=0,033). The three-component endpoint NT-proBNP + sST2 + Ptx-3 (LR=12,45, p=0,033) slightly prevailed over the combination of NT-proBNP and sST2. Thus, we demonstrated the efficiency of new biomarkers for 2-year cardiovascular events prognosis after MI.

The study limitations are a comparatively small sample pool and a short follow-up period, both limiting the statistical potential of analysis.

Relationships and Activities: none.

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Effect of intramyocardial haemorrhage on structural and functional echocardiographic parameters of myocardium after ST-segment elevation myocardial infarction with

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Aim. To analyze the effect of intramyocardial haemorrhage (IMH) on the structural and functional echocardiographic parameters of myocardium in patients with primary ST-segment elevation myocardial infarction (STEMI).

Material and methods. The study included 60 patients with primary STEMI reperfused within 12 hours after symptom onset. On the second day after the event, all subjects underwent gadolinium-enhanced cardiac magnetic resonance imaging (MRI). IMH was visualized as T2-weighted hypointense areas. Subsequently, all patients underwent the standard echocardiography on the 7th day after MI.

Results. IMH was revealed in 31 patients (51,6%). In 22 patients (70,9%), IMH was accompanied by microvascular obstruction (MVO). In the remaining 9 patients (29%), an isolated IMH phenomenon was visualized. Lower values of left ventricular ejection fraction (LVEF) and LV volume parameters were associated with a combination of MVO and IMH. At the same time, the indices of volumetric characteristics and LVEF in isolated IMH were the same as in the group without IMH and MVO. It was demonstrated that the IMH occupies 1% (1-3%) of the LV myocardium. Correlation analysis showed a moderate inverse correlation between the IMH area and LV contractile function: the larger the area, the lower the LVEF (R=-0,35; p=0,007).

Conclusions. The analysis of the influence of different IMH phenotypes on the structural and functional echocardiographic parameters of myocardium in the short-term period after STEMI has shown that the combination of IMH with MVO and isolated IMH have different effects on LV contractile function. The combination of IMH with MVO is a predictor of a decrease in LVEF and increase of end-systolic volume (ESV), while an isolated IMH does not affect these parameters. Correlations between the IMH area and a decrease in LVEF, as well as an increase in ESV, have been demonstrated.

Keywords: microvascular injury, intramyocardial haemorrhage, STEMI, myocardial infarction.

Relationships and Activities. This work was supported by a fellowship of the President of the Russian Federation for young scientists and post-graduate students “The influence of microvascular myocardial injury on the course of the inflammatory response in myocardial infarction”.

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The absence of microvascular perfusion, despite the restoration of blood flow in the epicardial coronary artery, is a limiting factor in reperfusion therapy in ST-segment elevation myocardial infarction (STEMI) [1]. The actualization of the problem of microvascular injury is largely associated with the magnetic resonance imaging (MRI) in patients after an acute coronary event. According to the studies conducted, contrast-enhanced cardiac MRI is a highly sensitive and specific method visualizing injury at damage at microvascular level [2].

To date, it is known that microvascular injury is heterogeneous and includes several phenomena: isolated microvascular obstruction (MVO), a combination of MVO with intramyocardial haemorrhage (IMH), and, according to recent data, isolated IMH. It should be noted that until recently IMH has always been associated with MVO [2]. However, recently Reinstadler SJ, et al. demonstrated the heterogeneity of IMH, since in addition to its combination with MVO, a group with isolated IMH was described [3]. Previously, we have also shown different phenoty pes of the IMH in patients with primary STEMI [4].

If MVO refers to the generally accepted predictors of pathological remodeling and progression of heart failure, then opinions on IMH are contradictory [5-9]. According to a meta-analysis with 9 studies, the prevalence of IMH is considered as more unfavorable a prognostic factor associated with decreased contractile function and pathological myocardial remodeling. In the studies, all patients had a combination of IMH with MVO [7]. There is also an opposite point of view, according to which IMH does not have a significant effect on myocardial remodeling [6]. The ambivalence of the obtained results shows that to date deficient knowledge regarding this phenomenon in an urgent issue. The question remains debatable whether IMH is only a 'satellite' or the cause of severe myocardial injury. In addition, it is of interest to study the heterogeneity of this phenomenon and assess the structural and functional cardiac parameters depending on the IMH phenotype.

The aim was to analyze the IMH effect on the structural and functional echocardiographic parameters of myocardium in patients with primary STEMI.

Material and methods

For the period from March 2018 to February 2019, 60 patients with primary STEMI who were admitted to the Cardiology Research Institute of the Tomsk National Research Medical Center in the first 12 hours from the onset were included in the study. All patients underwent urgent reperfusion of the infarct-related coronary artery. For coronary reperfusion, 2 methods were used — primary percutaneous coronary intervention (n=21) and pharmacoinvasive treatment (n=39). The choice of the reperfusion strategy was carried out at the prehospital stage according to the guidelines on STEMI [1]. The exclusion criteria were patient refusal, repeated MI, previous coronary revascularization, unstable hemodynamics, acute psychiatric disorders, severe comorbidities, and contraindications to cardiac MRI. All patients signed informed consent before inclusion. The study protocol was approved by the Biomedical Ethics Committee of the Cardiology Research Institute.

On the second day after the acute coronary event, all subjects underwent contrast-enhanced cardiac MRI on a Toshiba Vantage Titan scanner, with a magnetic induction of 1.5 T. MRI was performed on the basis of cardiac package Cardiac with obtaining myocardial images in synchronization of electrocardiography and respiration. For contrast study, a gadolinium-based contrast agent was used. The cardiac MRI protocol included standard pulse sequences (PIs) (T2-weighted dark blood sequence; fat-suppressed T1-weighted sequence) — along the short axis in a two-chamber view; dynamic sequences (GRE-SSFP 'bright blood' technique) — along the short axis in a two-chamber view, along the long axis in a two-, four-chamber view; delayed contrast-enhanced MRI (8-15 minutes after intravenous administration of a contrast agent) (GRE IR with selection of inversion time, TSE T1) — along the short axis in a two-chamber view, along the long axis in a two-, four-chamber view.

MI was assessed according to the following criteria: focal enhancement of the signal intensity on T2-weighted images, subendocardial contrasting of the myocardium or in varying degrees of transmurality of the left ventricular (LV) wall, on delayed contrast-enhanced and accumulation of contrast agent in myocardial segments of corresponding coronary arteries. IMH was visualized as hypointense areas against the background of the myocardium with increased signal intensity in the T2 weighted mode (Figure 1). MVO was defined as hypointense areas in the delayed contrasting phase.

Echocardiography was performed on a Vivid E9 ultrasound system (GE, Healthcare) in a two-dimensional mode according to the standard technique from the parasternal and apical views using a M5S matrix sector probe (1,5-4,6 MHz). Standard echocardiography was assessed 7 days after MI.

Statistical data processing. Statistical analysis of the data obtained was carried out using the

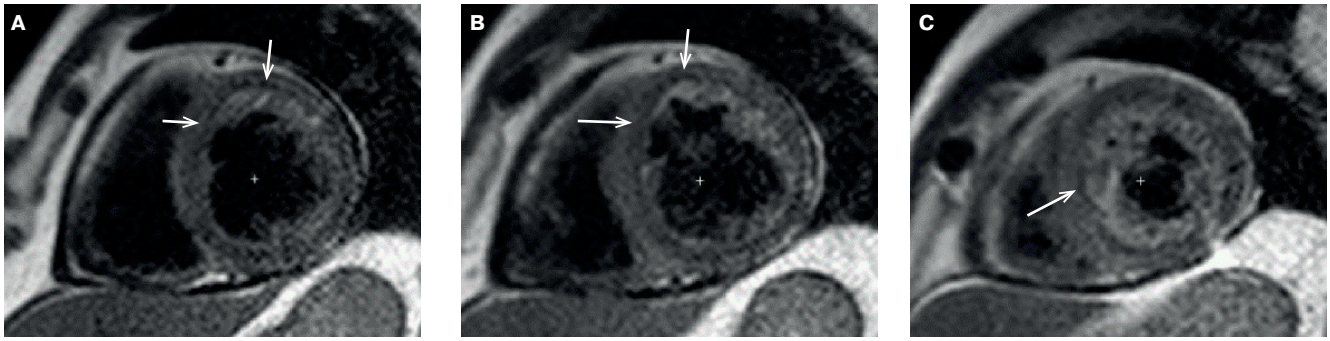

Figure 1. Intramyocardial haemorrhage by cardiac MRI. The short axis of the basal, middle, and apical (**A**, **B**, **C**) LV levels.
Note: arrows show hypointense areas in the projection of the LV anterior wall (**A**, **B**) and inferior lateral wall (**B**, **C**) in the T2-WI mode.

STATISTICA 10 software package. The obtained values are presented as the median (Me) and 25 and 75 percentiles (Q_{25};Q_{75}). The statistical significance of the differences between the two independent quantitative variables was assessed using the Mann-Whitney U test. The Kruskal-Wallis test was used to determine the significance of differences in multiple comparisons. The statistical significance of differences in qualitative traits was assessed using the Pearson's chi-squared test and Fisher's F-test. The strength of the relationship was determined using Spearman R correlation analysis. To assess the relationship of various factors, we used logistic regression methods. Differences between groups were considered significant at $p<0,05$.

Results

According to contrast-enhanced cardiac MRI performed on the second day after MI, the overall incidence of microvascular injury was 68,3% (n=41). In 10 patients, an injury was represented by an isolated MVO, which amounted to 16,7%. The IMH occurred in 31 patients (51,6%). Moreover, most often, in 22 patients (70,9%), IMHT was detected in combination with MVO. An isolated IMH was visualized in 9 patients (29%) out of 31. In 19 patients, there was no microvascular injury (31,7%), and these patients were selected as a comparison group (Figure 2).

Clinical and medical history characteristics of patients, depending on the presence of IMH, are presented in Table 1.

Earlier, we described in more detail the characteristics of groups depending on the phenotype of microvascular injury [4]. With enlarged sample and detailed IMH analysis, we obtained a similar result: large values of troponin I and myocardial injury area were observed in the IMH group. When dividing IMH into isolated and combination with MVO, it was the combination that contributed to the change of listed indicators. The previously described tendency to longer ischemia in IMH+MVO group also persists. According to coronary angiography, the no-reflow phenomenon occurred in three patients. All these cases belonged to IMH+MVO group according to MRI data. In addition, there was a tendency for more frequent no-flow in the epicardial artery (TIMI ⩽1) before angioplasty in IMH+MVO group compared with patients with no microvascular injury. A comparative analysis of the group with isolated IMH and without microvascular injury revealed significant differences in age and body mass index: the patients were older and with lower body weight.

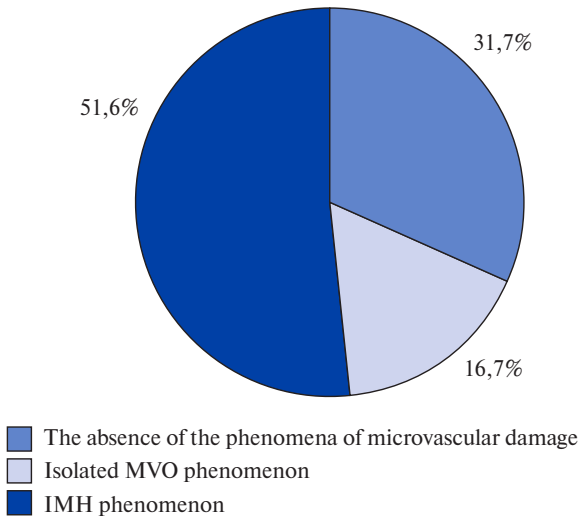

Figure 2. Prevalence of microvascular injury in patients with primary STEMI.
Abbreviations: IMH — intramyocardial haemorrhage, MVO — microvascular obstruction.

The structural and functional LV parameters according to echocardiography, depending on IMH presence in the early postinfarction period, are presented in Table 2. Regardless of the presence of microvascular injury, the integral indicators of echocardiography did not significantly differ from normal values. Perhaps this is due to the inclusion of non-severe patients and the early reperfusion therapy.

Table 1

Clinical and medical history characteristics of the patients included in the study depending on the presence of microvascular injury

Parameter	No microvascular injury, n=19	IMH, n=31	IMH	
			Isolated, n=9	Combination with MVO, n=22
Age (years)	59 (49-66)	60 (55-68)	65 (62-69)*	62 (55-65)
Sex (m/f)	15/4	23/8	6/3	17/5
BMI (kg/m^2)	26 (24-30)	27,4 (24,2-31)	25,01 (21,5-29,05)*	28,23 (26,7-31)
GRACE (%)	2 (1-3)	2 (1-4)	4 (2-5,5)	2 (1-4)
Onset-to-reperfusion time (min)	130 (91-160)	162 (100-275)	113 (100-179)	193 (95-400)
Reperfusion technique (PIS/primary PCI)	14/5	15/16	5/4	10/12
Localization of MI (n, %) Anterior Inferior	 10 (52,6) 9 (47,4)	 20 (64,5) 11 (35,5)	 4 (44,4) 5 (55,6)	 16 (72,7) 6 (27,3)
Killip (n, %) I II	 15 (78,9) 4 (21,1)	 24 (77,4) 7 (22,6)	 8 (88,9) 1 (11,1)	 16 (72,7) 6 (27,3)
Q-wave MI (n, %)	10 (52,6)	16 (51,6)	6 (66,7)	10 (52,6)
TIMI grade ⩽1 blood flow before PCI, (n, %)	1 (5,5)	10 (32,6)	2 (22,2)	8 (36,4)
No-reflow by CA after PCI, (n, %)	-	3 (9,6)	-	3 (13,6)
Throponin I, ng/l	4,66 (2,2-34,7)	38,2 (17,3-95,2)§	18,7 (17,3-22,8)	46,5 (14,9-98,8)†
Myocardial injury area according to cardiac MRI, %	10 (8-18)	24 (17,5-29)§	23,2 (9-25)	24,8 (17,5-35)†
Risk factors of CAD				
Hypertension (n, %)	18 (94,7)	28 (90,3)	8 (88,9)	20 (90,9)
Diabetes (n, %)	2 (10,5)	9 (29)	2 (22,2)	7 (31,8)
Dyslipidemia (n, %)	18 (94,7)	30 (96,7)	9 (100)	21 (95,5)
Obesity (n, %)	6 (31,6)	9 (29)	2 (22,2)	7 (26,3)
Smoking (n, %)	16 (84,2)	22 (70,9)	7 (77,8)	15 (68,2)
In-hospital therapy				
ASA+Clopidogrel (n, %)	7 (36,9)	14 (45,2)	5 (55,6)	9 (40,9)
ASA+ Ticagrelor (n, %)	12 (63,1)	18 (58)	4 (44,4)	14 (63,6)
ACE inhibitors (n, %)	17 (89,5)	29 (93,5)	7 (77,8)	22 (100)
β-blockers (n, %)	15 (78,9)	28 (90,3)	6 (66,7)	22 (100)
Statins (n, %)	19 (100)	31 (100)	9 (100)	22 (100)

Note: * — p<0,05 — difference between the group with isolated IM|H and the group without microvascular injury; § — difference between the group of IMH (total) and the group without microvascular injury; † — difference between IMH+MVO combination and the group without microvascular injury.

Abbreviations: ASA — acetylsalicylic acid, IMH — intramyocardial haemorrhage, ACE — angiotensin converting enzyme, MI — myocardial infarction, BMI — body mass index, CA — coronary angiography, MVO — microvascular obstruction, MRI — magnetic resonance imaging, PIS — pharmacoinvasive strategy, PCI — percutaneous coronary intervention.

The presence of IMH was independently associated with lower LV ejection fraction (LVEF) values (53,9% [48-60] vs. 64,5% [60-68]; p=0,002), an increase in end-systolic volume (ESV) (47 ml [35-61] vs. 35,5 ml [28,5-43]; p=0,02) and end-systolic volume index (ESVI) (25,3 ml/m^2 [19,4-32,9] vs. 19,5 ml/m^2 [16,1-22,4], p=0,005), in contrast to patients without microvascular injury (Table 2). When assessing end-diastolic dimension, significant differences between the groups were not found. The values of the impaired local contractility index were higher in the group with IMH (2,22 [2,0-2,5] vs. 2,44 [2,25-2,75]; p=0,007).

When dividing patients into groups of isolated IMH and a combination of IMH with MVO, a different effect on myocardial contractile function and LV volume was found. Lower values of LVEF (52% [48-58] vs. 64,5% [60-68]) and an increase in ESV (53 ml [40-66] vs. 35,5 ml [28,5-43]), ESVI (28,2 ml/m^2 [22,3-33,7] vs. 19,5 ml/m^2 [16,1-22,4])

Table 2

Echocardiographic data on the seventh day from primary STEMI, depending on IMH presence

Parameter	No microvascular injury, n=19	IMH, n=31	IMH	
			Isolated, n=9	Combination with MVO, n=22
LVEF, %	64,5 (60-68)	53,9 (48-60)†	64 (58,5-66)	52 (48-58)*
EDV, ml	93,5 (80,5-108)	100 (89-120)	92 (86-105)	115 (95-133)
ESV, ml	35,5 (28,5-43)	47 (35-61)†	33,5 (31,5-39,5)	53 (40-66)*
EDVI, ml/m^2	49,9 (43,5-54,3)	54,2 (46,8-60,6)	49,3 (45,2-56,6)	57,2 (50,9-67,7)
ESVI, ml/m^2	19,5 (16,1-22,4)	25,3 (19,4-32,9)†	19,1 (16,6-23,3)	28,2 (22,3-33,7)*
ILCI, CU	1,22 (1,0-1,5)	1,44 (1,25-1,75)†	1,19 (1,19-1,44)	1,44 (1,12-1,75)*
SV, ml	58 (48-67)	58 (47-65)	57 (53-66,5)	60 (49-75)
MM, g	197,5 (167-232)	204 (174-240)	176,5 (169-206)	208 (181-243)
MI, g/m^2	97 (93-123)	107 (96-127)	103 (92-109)	113 (98-133)

Note: † — p<0,05 — difference between the group without microvascular injury and the IMH group (total); * — p<0,05 — difference between the group without microvascular injury and the isolated IMH group.

Abbreviations: IMH — intramyocardial haemorrhage, MVO — microvascular obstruction, LVEF — left ventricular ejection fraction, EDV — end-diastolic volume, ESV — end-systolic volume, EDVI — end-diastolic volume index, ESVI — end-systolic volume index, ILCI — impaired local contractility index, SV — stroke volume, MM — myocardial mass, MI — mass index.

were associated with a combination of MVO and IMH. At the same time, volume characteristics and LVEF in isolated IMH were comparable with the group without microvascular injury. Similar results were demonstrated in the analysis of impaired local contractility index. The impaired local contractility index was significantly higher in the MVO+IMH group; with isolated IMH, such a correlation was not observed.

Using logistic regression analysis, it was shown that IMH+MVO combination is a predictor of decreased LV contractile function in the early postinfarction period (odds ratio, 2,1; 95% confidence interval, 2,02-2,19; p=0,005). The effect of isolated IMH on LVEF did not reach statistical significance (2,08; 0,99-2,18; p=0,07).

In addition to the very fact of IMH presence, the effect of its area on LV contractility was assessed. IMH to LV area was 1% (1-3%). The IMH area was comparable both in combination with MVO and in the isolated type: 1% (0,6-2,2) vs. 1% (0,7-2,4).

Correlation analysis showed a moderate inverse correlation between the IMH area and LV contractile function: the larger the IMH area, the lower the LVEF (R=-0,35; p=0,007) (Figure 3). Evaluating separately the effect of IMH area on LVEF in the isolated type, such a dependence was not revealed, however, this may be due to the small sample. Direct positive correlations of IMH with ESVI (R=0,29; p=0,02) were established, which were also not confirmed in patients with isolated IMH (Figure 4).

Discussion

Despite the fact that microvascular injury in myocardial infarction has been studied in many aspects, the study of the IMH phenomenon remains relevant. Until now, the mechanism of its phenomenon remains unclear, and discussions continue whether it is the cause or the result of ischemia-reperfusion Injury. According to the most common point of view, the development of IMH is associated with irreversible MVO, and therefore it is associated with severe microvascular dysfunction [7, 10-13].

The prevalence of the IMH, according to the studies, is wide. This phenomenon is observed in 30-60% of patients with STEMI [10, 13]. According to our study, IMH was detected in 51,6% of cases. It has been demonstrated that IMH is heterogeneous and is most often associated with MVO. However, in 15% of cases, an isolated IMH was encountered. Similar data on the imaging of isolated IMH were described in the only recently published study by Reinstadler SJ, et al., where IMH without MVO was detected in 2% of patients [3]. A targeted study of this IMH phenotype has not been carried out. Analyzing the cause for higher prevalence of isolated IMH in the study performed, the relationship was suggested between the use of a pharmacoinvasive treatment and development of isolated IMH, but no correlations were obtained, which may be due to a small sample. The second possible explanation is the limitation of the T2 mode, which was used in our

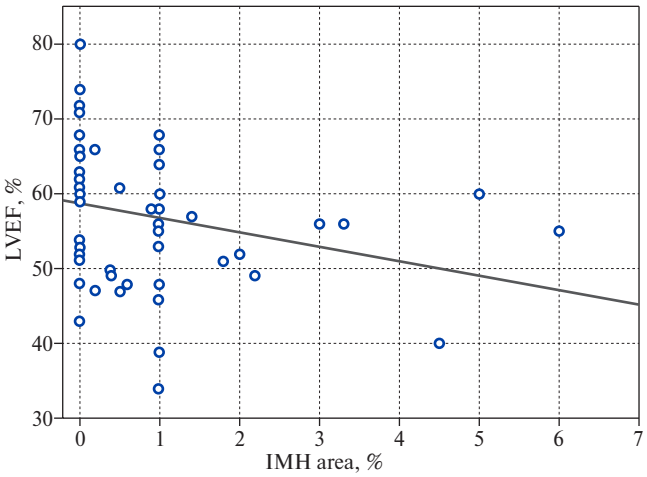

Figure 3. Relationship between the IMH area and LVEF according to echocardiography 7 days after MI.
Abbreviations: IMH — intramyocardial haemorrhage, LVEF — left ventricular ejection fraction.

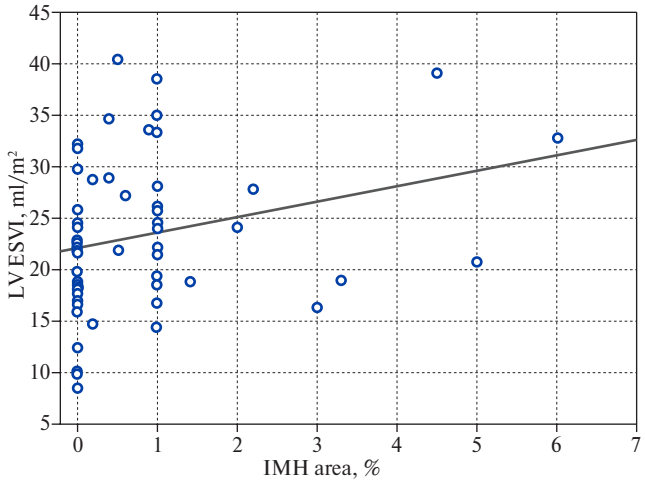

Figure 4. Relationship between the IMH area and LV ESVI according to echocardiography 7 days after MI.
Abbreviations: IMH — intramyocardial haemorrhage, LVEF — left ventricular ejection fraction.

study, since it was proved that T2* is more sensitive and specific for IMH imaging [11].

When planning this study, we expected that IMH would lead to a significant deterioration in contractility and a rapid progression of pathological myocardial remodeling. Analysis of the results showed that a decrease in LVEF and an increase in LV volume parameters independently correlate with combination of IMH with MVO. The revealed regularities confirm the published data on the effect of IMH on LV contractility, since in the conducted studies IMH was found in all cases in combination with MVO; therefore, IMH predicted decreased LVEF, as well as with progressive structural abnormalities [2, 11-13]. Fundamentally new is that in the group of isolated IMH, on the contrary, there was no effect on LV contractility and volume parameters. In addition, the structural and functional cardiac parameters according to echocardiography in isolated IMH group were comparable to the group without microvascular injury.

It has been demonstrated that IMH to LV area is 1% (1-3%). However, despite the small size of IMH, studies have shown that the very fact of IMH is associated with a large MI size, pathological remodeling, systolic dysfunction, and an unfavorable clinical outcome. It is important to note that these patterns were also established when studying the IMH with MVO combination [2, 7, 13]. In this connection, a number of authors believe that the assessment of MVO and its area play a more significant role in healing of the infarcted area and myocardial remodeling. Thus, Ma M, et al. showed that the MVO size, regardless of IMH presence and size, has a more pronounced correlation with damaged myocardial size [6]. The effect of isolated IMH area on LVEF was not evaluated in any of the studies. According to our work, it has been shown that if the phenomena are not divided into isolated and combination, the IMH area correlates with decreased LVEF and increased LV ESVI. However, with a targeted examination of isolated IMH area on LV structure and function, similar dependences are not shown.

The study of cardiac MRI in patients with MI as a diagnostic tool is a relatively new direction in cardiology. The ability of this method to non-invasively visualize different phenotypes of microvascular injury *in vivo* demonstrated the existing barrier to studying the myocardial remodeling. In this regard, the following questions are relevant: an isolated IMH and a combination of IMH with MVO are links of one process and the appearance of which of the phenomena of microvascular injury or just their combination is more associated with pathological myocardial remodeling, as well as how we can influence microvascular injury? It is likely that the extravasation of erythrocytes into the myocardium, which is the basis of IMH, is only a trigger mechanism that provokes a cascade of reactions leading to pronounced structural and functional cardiac changes. Therefore, it is of interest to further study the IMH, especially in terms of its effect on chronic sterile inflammation.

Study limitations. A small number of subjects in the group of isolated IMH; no technical feasibility of using T2* MRI mode.

Conclusion

The analysis of the influence of different IMH phenotypes on the structural and functional echocardiographic parameters of myocardium in the short-term period after STEMI has shown that the combination of IMH with MVO and isolated IMH have different effects on LV contractile function. The combination of IMH with MVO is a predictor of a decrease in LVEF and increase of ESV, while an isolated IMH does not affect these parameters. Correlations between the IMH area and a decrease in LVEF, as well as an increase in ESV, have been demonstrated.

Relationships and Activities. This work was supported by a fellowship of the President of the Russian Federation for young scientists and post-graduate students "The influence of microvascular myocardial injury on the course of the inflammatory response in myocardial infarction".

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Experience in using focused cardiac ultrasound in patients with acute heart failure in the intensive care unit

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Portable ultrasound devices in initial cardiac patient examination in intensive care units are seen as an essential addition to conventional physical examinations.

Aim. To assess the potential of using focused cardiac ultrasound for patients admitted in the intensive care unit with a clinical performance of acute heart failure.

Material and methods. The study included 180 patients, 110 of whom were men. The mean age was 57 (40;74) years. The patients included in the study were divided into 2 groups: group 1 consisted of patients who, upon admission, underwent a general clinical examination and an ultrasound with a portable device; group 2 — patients who, upon admission, underwent only a conventional examination. Using portable ultrasound scanners, the doctors evaluated ventricular contractility, the presence of significant valve regurgitation, the diameter and degree of inferior vena cava collapse, as well as the presence, prevalence and number of B-lines. The differences in the time required for the diagnosis using various methods were determined. Structural changes in the heart and lungs, identified using a portable ultrasound device, were also assessed.

Results. In the group of patients who underwent focused cardiac ultrasound, the time from admission to initiation of therapy was 11 (7;18) minutes. In the group 2, the median time from admission to initiation of intravenous diuretic administration was 86 (52;116) min (p<0,001). According to the results of an ultrasound with a portable device, the following changes were noted: significant left ventricular contractility decrease were found in 32,4% of patients; a decrease in right ventricle contractility — in 16,2%. In 50% of patients, the left ventricular contractility was sufficient. In 43,3% of patients, bilateral B lines were identified as a sign of interstitial pulmonary syndrome; in 38,8%, there were signs of hypervolemia when assessing the inferior vena cava. Hemodynamically relevant mitral regurgitation was noted in 28,8% of cases; hemodynamically relevant tricuspid regurgitation — 21,1%; relevant aortic regurgitation — 6,6%. In 10% of patients, there was restricted mobility of aortic valve leaflets, which was suspected as aortic stenosis. In 18% of cases, no significant intracardiac hemodynamic changes were noted.

Conclusion. It has been shown that examination with focused cardiac ultrasound in the intensive care unit reduces decision time by more than an hour. Initial examination of a patient with acute heart failure using pocket cardiac ultrasound devices reveals clinically relevant intracardiac hemodynamic disorders.

Keywords: focused cardiac ultrasound, assisted examination, acute heart failure, portable ultrasound systems.

Relationships and Activities: none.

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The possibilities of clinical use of assisted examination with ultrasound diagnostic methods in cardiac patients are regulated and listed in a consensus paper of the European Association of Cardiovascular Imaging (EACVI) [1]. Pocket ultrasound systems are modern portable handheld systems that represent a smartphone, or a tablet and a transducer, or transducers that are synchronized with mobile devices [2]. These are convenient systems for routine practice that a physician can place in the pocket of work clothes, constantly carry with him/her, and use them in his/her work. Pocket ultrasound systems are very easy to use and have a simple and self-explanatory user interface (Figure 1). Mobile ultrasound systems make it possible to scan in both two-dimensional mode and color Doppler imaging; some systems allow using a one-dimensional mode. The available measurements are limited to measuring the distance and area; for these reasons, a mobile ultrasound system cannot provide an accurate quantitative assessment of the contractility and volumetric parameters, as well as velocity characteristics of transvalvular flows. In all the existing limitations, scanning is carried out in real-time, the images have optimal quality, which makes it possible to answer a specific clinical question in most cases [3]. The main advantage of handheld devices is that they are easy to be carried; so, they can be easily accessible to specialists in various situations anywhere: in the ward, at the patient's bedside, and during transportation that provide improvement of the quality of medical care. Using mobile ultrasound devices in the primary assessment of a patient in Cardiac Intensive Care Units is increasingly considered to be a significant addition to the traditional physical examination of the cardiovascular system [4].

The purpose of the study is to assess the possibility of reducing the decision-making time in a focused cardiac ultrasound in patients admitted with a clinical presentation of acute heart failure (AHF) in the Intensive Care Unit (ICU) for cardiac patients of the City Clinical Hospital Named After S. S. Yudin of the Moscow City Health Department.

Figure 1. Pocket ultrasound systems.

Material and methods

180 patients were included in the observational study; the number of males was 110. The patients' average age was 57 (40;74) years old. In admission, 27,7% of patients (n=50) had atrial fibrillation rhythm disorders, and 67,7% of patients (n=122)

Table 1

General characteristics of patients upon admission to the hospital

Parameter	All patients (n=180)
Age, years	57 (40;74)
Males, n (%)	110 (61,1)
Diagnosis of AHF, n (%)	180 (100)
AF, n (%)	50 (27,7)
ACS, n (%)	122 (67,7)

Note: the data are presented as a median and an interquartile range (Q1; Q3), as well as in absolute numbers (n) and shares in percentages (%).

Abbreviations: ACS — acute coronary syndrome, AHF — acute heart failure, AF — atrial fibrillation.

Table 2

Time intervals (minutes) from the patient admitting to the hospital until obtaining US results

Parameter	Focused cardiac ultrasound by a cardiologist	US examination performed by a physician of instrumental diagnostics	p
Minutes	11 (7;18)	86 (52;116)	<0,001

Note: the data are presented as a median and an interquartile range (Q1; Q3).

Abbreviation: US — ultrasound.

Table 3

Treatment and diagnostic measures initiated based on the results of the focal ultrasound examination

Parameter	Patients (n=90)
Diuretic infusion, n (%)	54 (60)
CT angiography, n (%)	4 (4,4)
Emergency consultation with a cardiac surgeon upon admission, n (%)	6 (6,6)

Note: the data are presented as a median and an interquartile range (Q1; Q3), as well as in absolute numbers (n) and shares in percentages (%).

Abbreviation: CT — computed tomography.

were diagnosed with the acute coronary syndrome at the prehospital stage (Table 1).

In the Cardiac Intensive Care Unit, several specialists completed additional training for 36 hours on the use of targeted diagnostic focal ultrasound in emergency cardiology. As an additional procedure to the primary clinical examination of patients, these physicians could use pocket ultrasound systems to more precisely define the parameters of intracardiac hemodynamics.

The patients who participated in the study were divided into 2 groups. The patients of the first group, upon admission, underwent a general clinical examination combined with an objective assessment of the parameters of intracardiac hemodynamics with the help of a focal US mobile device. The patient of the second (control) group, who were subsequently selected, upon admission, underwent a general examination without additional focal US examination. Patients of the control group were managed according to the standard protocol, with the engagement of specialists of instrumental diagnostics, who performed ECG examination at the patient's bedside.

As part of an focused cardiac ultrasound, physicians evaluated the following parameters: ventricular hypocontractility; significant regurgitant flows on the mitral, aortic, and tricuspid valves; the inferior vena cava diameter and degree of its collapse; and interstitial pulmonary syndrome in terms of its prevalence and number of B-lines that are determined by moving the US transducer along the surface of the patient's chest over the entire pulmonary fields at the appropriate points. The differences in the time intervals were determined, during which the diagnosis was confirmed using US data (obtained by a pocket handheld device or a standard method of examination) and specific therapy was initiated. Also, changes in intracardiac hemodynamics were assessed, which were determined by focal US examination of the heart and lungs using a mobile device.

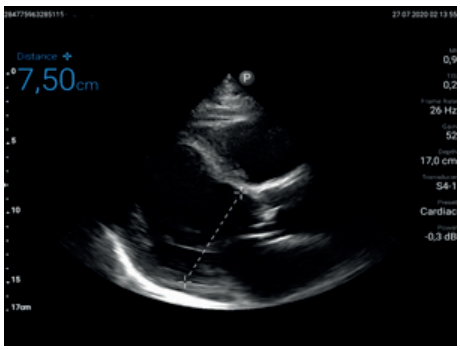

Figure 2. LV dilation according to the focused cardiac ultrasound.

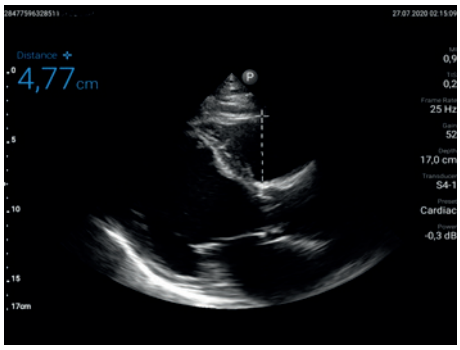

Figure 3. Dilation of the RV outflow tract according to the focused cardiac ultrasound.

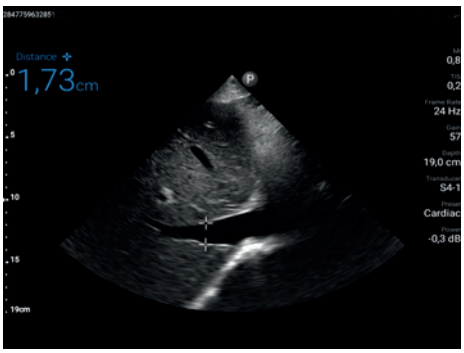

Figure 4. Assessment of the patient's volemic status according to the focused cardiac ultrasound.

Results

The time intervals were assessed, according to the records in the case history, after what period from admission information on the parameters of intracardiac hemodynamics was available, based on which the subsequent therapeutic and diagnostic tactics were selected. In the patient group who underwent a focused cardiac ultrasound, a median was 11 (7;18) minutes. In the patient group where a specialist of diagnostic services was required, the median of the time interval from the patient

admission to the hospital to the obtaining ultrasound results was 86 (52;116) minutes (p<0,001) (Table 2).

In the patients who underwent a US examination with a mobile ultrasound system, the following changes were perceived: 32,4% of patients (n=40) had significant violations of the left ventricle (LV) contractility, and 16,2% of patients (n=20) had right ventricular (RV) hypocontractility. 50% of patients (n=45) had LV contractility that was considered to be satisfactory. In 43,3% of patients (n=39), bilateral B-lines were identified as a symptom of the interstitial pulmonary syndrome, and in 38,8% of patients (n=35) had symptoms of hypervolemia when assessing parameters of the inferior vena cava. Hemodynamically significant mitral regurgitation was in 28,8% of patients (n=26); hemodynamically significant tricuspid regurgitation was in 21,1% of patients (n=19), and significant aortic regurgitation was in 6,6% of patients (n=6). Mitral stenosis was detected in 3,3% of patients (n=3), and a significant limitation of the mobility of the aortic valve cusps, which allows suspecting aortic stenosis, was detected in 10% of patients (n=9). No significant changes in the parameters of intracardiac hemodynamics were revealed in 18% of patients (n=20).

Based on the results of the focal US examination, the following therapeutic and diagnostic measures were initiated in the first hour of the patient's stay in the hospital: therapy with intravenous diuretics was immediately started in 60% of patients (n=54); 9,9% of patients (n=9) were urgently referred for computed tomography (CT) — angiography; 6,6% of patients (n=6) were consulted by a cardiac surgeon and transferred to the Surgical Department to perform emergency cardiac surgery (Table 3).

Discussion

Patients with AHF or acute decompensated heart failure (ADHF) represent a significant portion of all patients in Cardiac Intensive Care Units. AHF is a clinical syndrome characterized by a combination of symptoms (breathlessness; orthopnea; edema of the lower extremities) and signs (increased pressure in the jugular veins; lung congestion), often caused by structural and/or functional heart disorders leading to a decrease in LV contractility and/or an increase in LV filling pressure [5-8]. The time of therapy initiation is an important question in the treatment of patients with AHF and ADHF, and the question is uncertain until now. At present day, little information is available on whether there is a therapeutic window in AHF treatment that can improve long-term outcomes, and patients with different stages of cardiac functional decompensation are causing heterogeneity in clinical trials. Unlike studies devoted to the treatment of acute myocardial infarction, the concept of a "golden hour" for treating AHF has not yet been defined. Data from the ADHERE (Acute Decompensated Heart Failure National Registry) show that earlier initiation of therapy can improve long-term outcomes [9]. The authors of the concept of the earliest possible administration of an intravenous diuretic believe that the delay in therapy may explain the increased mortality since AHF provokes the development of multiple organ failure and the need to use vasoactive medications in higher doses, as well as a higher likelihood of adverse effects [9]. In REALITY-AHF, a prospective multicenter observational cohort study, in patients admitted to the emergency department for AHF, early treatment with intravenous loop diuretics was associated with lower in-hospital mortality [10]. Data from this study showed that early initiation of intravenous treatment with furosemide significantly reduced in-hospital mortality.

Echocardiography performed with a pocket handheld device does not provide a comprehensive non-invasive assessment of intracardiac hemodynamics, but it allows assessing the presence of signs that are pathognomonic for AHF [11]. Evaluation of the severity of cardiac dysfunction and congestion using pocket US systems allows initiating the therapy with diuretics and/or vasodilators in the shortest possible time. This was shown in our study: the initiation time of medication therapy in the case of a focused cardiac ultrasound was reduced by more than 60 minutes. Considering this fact, the possibility of a focused cardiac ultrasound is an important component of a comprehensive assessment of a patient with a clinical presentation of AHF and contributes to making a quick clinical decision.

When analyzing the changes that were identified with the help of the pocket US device, several features were revealed. In particular, it is remarkable that 50% of patients retained the LV myocardial contractility. These data are consistent with the ADHERE, the largest international registry, according to which up to 55% of patients with AHF or ADHF have a preserved ejection fraction [12]. By carrying out focal echocardiography, LV dysfunction was revealed in 32,4% of patients (Figure 2), and LV dysfunction was revealed in 16,2% of patients (Figure 3), which also contributed to the acceleration of decision-making, for example, about transporting the patient to the X-ray operation room or for carrying out CT angiography. Focal ultrasound with a pocket device allows evaluating the patient's volume status when examining the size and degree of collapse of the inferior vena cava (Figure 4). This method quickly helps to objectify the symptoms of lung congestion,

such as interstitial pulmonary syndrome and inferior vena cava dilatation with its unsatisfactory collapse. The presence of these signs, in combination with clinical symptoms, allows making a differential diagnosis for breathlessness, diagnosis of heart failure, and initiation of medication therapy. Focal US examination with pocket handheld devices does not allow assessing the velocity characteristics of transvalvular flows. The ability of these systems in the diagnosis of valve stenosis lies only in the qualitative visual characteristic of limiting the mobility of the valve cusps. Currently, the work on studying this problem to assess the short-term and long-term outcomes in patients whose management tactics have changed with the introduction of focused cardiac ultrasound is being continued in the clinic. Our results showed the importance of using mobile US devices for making clinical decisions in emergencies suggesting an additional possibility for direct and indirect resource savings if US examination is more routinely and earlier included in making a clinical decision. The limitation of the competence of physicians in Cardiac ICUs in using and interpreting these US methods is a problem of widespread implementation of the focal protocol. Modern educational programs and medical schools increasingly combine focused cardiac ultrasound training in training modules. Our study provides additional evidence that using mobile ultrasound systems in the Cardiac ICUs can shorten the time for making clinical decisions, especially in the context of a City Clinical Hospital.

In the group of patients with suspected AHF who underwent a focused cardiac ultrasound with the help of mobile systems, medication therapy was initiated in 11 minutes. In the patient group where a specialist of diagnostic services was required, medication therapy was initiated in 86 minutes.

Conclusion

The introduction of mobile US systems into cardiologists' clinical practice is a reflection of modern trends towards miniaturizing diagnostic facilities. A clinician's ability to perform a focused cardiac ultrasound allows shortening the time for making a clinical decision and improving the quality of health care for patients in the ICU. It is necessary to carry out further clinical studies devoted to the optimal scenarios for the implementation of using mobile US systems in clinical practice.

Relationships and Activities: none.

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Comparative analysis of cardioprotective effects of two renal denervation techniques

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Aim. To compare cardioprotective effects of two renal denervation (RD) techniques: main renal artery or its branches after bifurcation in patients with resistant hypertension (RH).

Material and methods. This randomized double-blind clinical (ClinicalTrials.gov. identifier: NCT02667912) study with a follow-up of 12,3±1,6 months included 55 patients with RH, which was divided into 2 groups: group 1 (n=27) — main renal artery denervation; group 2 — RD of branches. Mean age of patients was 57,3±9,5 and 56,4±9,3 years, respectively. We assessed structural and functional cardiac characteristics using two-dimensional speckle-tracking echocardiography (STE).

Results. Initially, the patients in the groups did not differ in terms of studied parameters and therapy. After RD in both groups, the levels of myocardial stress significantly decreased; 95% confidence interval: after main renal artery denervation — systolic [-4802; -2896], diastolic [-3264; -2032] dyne/cm^2; after RD of branches — [-6324; -5328] and [-4021; -2521] dyne/cm^2, respectively (p=0,001 and 0,024, respectively). After main renal artery denervation, there was a decrease in the left ventricular (LV) wall thickness (interventricular septum [1,06; -0,62] and posterior wall [0,12; -0,62]) in comparison with RD of branches ([-0,68; -1,28] and [-0,68; -1,06], respectively). These differences were significant: p=0,023 and 0,021, respectively. After distal RD, decrease in the LV mass was observed more often by 21,2%, an increase in the LV mass was 2 times less frequent. Restoration of diastolic function was more common in patients after distal RD than main renal artery denervation (26% vs 13%, respectively). According to pilot analysis, STE parameters was also improved.

Conclusion. Twelve months after distal RD, compared with the main renal artery denervation, the LV wall thickness, number of patients with LV hypertrophy, and diastolic dysfunction decreased significantly greater. Two-dimensional STE revealed improvement of cardiac parameters. The results require further research.

Keywords: heart, hypertension, renal denervation, diastolic function.

Relationships and Activities. State assignment of Tomsk National Medical Research Center (state registration: AAAA-A17-117052310076-7 dated 23.05.2017).

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Trial ID: NCT02667912 (https://clinicaltrials.gov/ct2/show/NCT02667912).

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According to the May Measurement Month global campaign, where 1,5 million people were examined in 2018, 33,4% were diagnosed with hypertension (HTN). Of 60% of participants observed for HTN, target blood pressure (BP) levels were achieved only in 33,2% [1]. The problem of reaching target pressure levels is an independent task for reducing the risk of cardiovascular events, which has not yet been resolved. For its implementation, in addition to drug therapy for HTN, novel therapy options (device-based treatment) are currently being proposed and actively studied [2]. Among them, the most widespread is the method of endovascular renal denervation (RDN) [3]. Various approaches to radiofrequency ablation are of great interest: conventional RD (CRD), used until 2016, with the application of ablation points in the renal artery trunk, and distal RD (DRD) when the ablation is carried out in its distal part and branches after the bifurcation. It was proved that it is in the distal renal artery and its branches the concentration of sympathetic nerve endings is maximal [4]. This was followed by studies that showed a more pronounced antihypertensive effect of DRD compared to CRD [5]. In this connection, there are grounds to believe that organ protection after DRD will be more beneficial, since the association between heart disorders and increased activity of the sympathetic nervous system [6], HTN and related myocardial stress (MS) is obvious. Beneficial CRD effects on the heart have been demonstrated previously in experimental and clinical studies [7-9]. There are practically no comparative studies concerning the cardioprotective effects of the two approaches. Therefore, the aim of this prospective randomized double-blind study was to compare the cardioprotective effects of CRD and DRD in patients with resistant hypertension (RH) in parallel groups.

Material and methods

This clinical (ClinicalTrials.gov.identifier: NCT02667912), single-center, randomized, double-blind, controlled in parallel groups study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The study protocol and informed consent, which was signed by each participant prior to study initiation, were approved by the Ethics Committees of all participating clinical centers.

There were following inclusion criteria: adult male and female patients aged 18-80 year with systolic blood pressure (SBP) ⩾160 mm Hg or diastolic blood pressure (DBP) ⩾100 mm Hg received the therapy (at least 3 months) with three antihypertensive drugs, including a diuretic. Exclusion criteria were as follows: glomerular filtration rate <30 ml/min/1,73 m^2, 24-hour mean SBP <135 mm Hg, secondary HTN, severe arterial abnormalities, pregnancy, significant failure of organs or systems (neurological, hematological, metabolic, cardiac, hepatic, pulmonary, etc.). Standard echocardiographic and left ventricular (LV) diastolic function (DF) indices, as well as two-dimensional strain speckle tracking echocardiographic (STE) parameters were evaluated [10-12]. LV MS was calculated as follows: MS_{syst} (MS_{diast}) = SBP (DBP) × LV end-systolic (diastolic) dimension / 4 × LV posterior wall thickness (PWT) × (1 + LV PWT / LV end-systolic (diastolic) dimension), dyn/cm^2. The technique of performing ORD and DRD in this study was described in detail earlier [13].

The study design is shown in Figure 1. The composition of drug groups and the doses prescribed were monitored at each visit to the center. Patients with RH (n=55), meeting the selection criteria, after angiography with ruling out of exclusion criteria disorders before the initiation of the RD were randomized in a 1:1 ratio into groups for radiofrequency ablation by the DRD or CRD. The type of intervention remained unknown to patients, researchers, and others involved in evaluating treatment outcomes throughout the study period. By the end of the study, four patients died for reasons unrelated to the procedure, while three patients refused to repeat examinations.

Statistical analysis was carried out using Statistica for Windows 10.0 software. The quality of the data was assessed using distribution histograms. In the case of pronounced deviations from the random distribution, the data were checked for errors in values and patient selection criteria. The hypothesis of a Gaussian distribution was tested using the Kolmogorov-Smirnov test. The main methods of statistical analysis were parametric Student's t test and the nonparametric Wilcoxon test for quantitative variables. The statistical significance of qualitative differences was assessed using the goodness of fit test; for values <10, the Yates' correction was used. When comparing the distributions of qualitative traits in dependent samples, the McNemar's test was used. The results are presented with the correct distribution: as mean ± standard deviation (M±SD) or as Me (median), confidence intervals (CI) or min-max values for informative presentation of data in case of incorrect distribution. The difference was considered significant at $p<0,05$.

Results

Patients in the groups did not initially differ in analyzed, anthropological indices, as well as in parameters of fundamental importance for the study (Tables 1, 2).

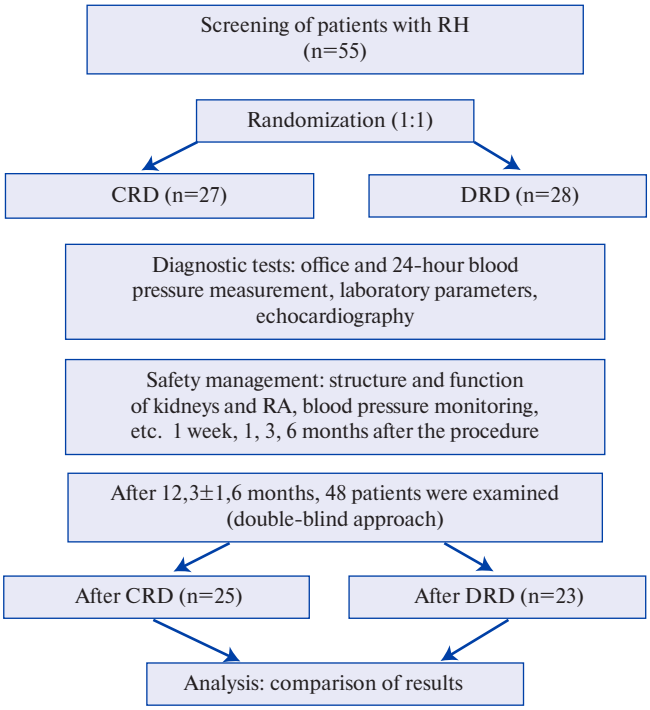

Figure 1. Study design.
Abbreviations: BP — blood pressure, DRD — distal renal denervation, CRD — conventional renal denervation, RA — renal artery, RH — resistant hypertension.

Table 1
Clinical characteristics of patients in a randomized trial

	CRD group	DRD group	P
Mean 24-hour SBP, mm Hg	158,0±15,2	166,3±24,2	0,122
Mean 24-hour DBP, mm Hg	87,9±17,6	90,8±18,6	0,781
Age, years	57,3±9,5	56,4±9,3	0,909
Sex, female %	62,0	60,0	0,248
Race, white %	100	100	1,000
Body mass index	32,3±4,2	31,2±5,3	0,623
COVID-19, %	11,4	12,7	0,522
Hypercholesterolemia, %	63,1	65,7	0,674
HR, bpm	71,1±9,8	69,7±12,0	0,308
GFR, ml/min/1,73 m^2	72,4±12,1	80,7±23,0	0,064

Abbreviations: DBP — diastolic blood pressure, DRD — distal renal denervation, CRD — conventional renal denervation, SBP — systolic blood pressure, GFR — glomerular filtration rate, HR — heart rate.

The initial values indicated the increase of interventricular septum (IVS) and LV PWT in patients with LV dimensions closer to the upper boundaries or exceeding the norm. Attention was drawn to a slight increase in the left atrial dimension and volume, which is typical for patients with RH. It should be noted that the analysis of 2D strain STE parameters was carried out as a pilot in a little part of the participants under CRD (n=4) and DRD (n=6). Nevertheless, initially there was a slight decrease in STE parameters relative to the general healthy population or approaching the lower normal limits (Table 2).

Patients used different groups of drugs, but without significant differences in the main classes at baseline (Table 3). The doses in the study groups were focused on the maximum tolerated for each participant. The researchers did not change therapy during follow-up.

To avoid duplication, previously published data on a more pronounced antihypertensive effect of DRD as compared to CRD on office and 24-hour BP are not presented here [13], which were used to calculate MS. When analyzing the parameters of systolic and diastolic MS, there was a positive trend in both groups (95% CI, systolic MS [-4802; -2896], diastolic MS [-3264; -2032] after CRD vs. [-6324; -5328] and [-4021; -2521] dyn/cm^2 after DRD, p=0,001 and 0,024, respectively), with a significantly greater decrease in systolic MS in the DRD group, which is clearly shown in Figure 2 with their median values.

A less significant decrease in LV wall thickness after CRD was noted (Me is shown in the figure): IVS min-max [-0,62; 1,06] and LVPW [-0,62; 0,12] compared with DRD: [-1,28; -0,68] and [-1,06; -0,68] (Figure 3).

Therefore, a more pronounced regression of estimated value is natural — LV mass with a tendency to superiority of DRD vs. CRD, but without a significant advantage. LV mass dynamics were as follows: -36,10 [-111,43; 23,42] and -5,46 [-86,39; 23,34], p=0,114, respectively. An illustration of LV mass distribution in the groups is presented in Figure 4, where the decrease in LV mass after DRD occurred more often by 21,2% (p=0,023). After DRD, an increase in LV mass occurred 2 times less often (patients with LV mass dynamics >0 g).

LV DF was analyzed with total assessment of diastolic dysfunction signs and showed improvement in both groups (Figure 5), but normalization of DF was achieved 2 times more often after DRD vs. CRD (26% vs. 13%, respectively). It should be noted that there was no high-grade (grade 3) dysfunction in the groups at baseline, and it was not detected after a 1-yearf follow-up.

Figure 6 A shows changes in 2D strain STE parameters for standard LV segments. Significant positive changes in of global longitudinal strain were detected, evident for the basal and apical segments, and the radial strain, where significant differences were observed in most segments after

Table 2

Comparative characteristics of initial echocardiography parameters during randomization

	CRD group, Mean±SD or Mean [5-95%]	DRD group, Mean±SD or Mean [5-95%]	P
Left atrial dimension, mm	43,17±5,14	43,04±3,78	0,521
Left atrial volume, ml	77,91±19,19	84,14±15,89	0,394
LV EDD, mm	47,19±5,14	47,53±2,95	0,325
LV ESD, mm	29,93±4,34	30,52±2,43	0,242
IVS, mm	14,2 [13,1-15,3]	14,1 [13,3-14,9]	0,184
LVPW, mm	12,8 [12,0-13,8]	12,8 [12,0-13,7]	0,389
LV mass, g	259,8 [236,4-293,2]	264,1 [240,0-288,7]	0,136
Global longitudinal strain, %	-13,9±5,01	-14,1±5,01	0,647
Strain in radial direction, %	46,43±14,88	44,11±9,91	0,521
Strain in circumferential direction, %	-15,72±6,61	-16,21±8,13	0,512
Strain rate longitudinal, sec $^{-1}$	1,137±0,286	0,992±0,230	0,385

Abbreviations: DRD — distal renal denervation, LVPW — left ventricular posterior wall, EDD — end-diastolic dimension, ESD — end-systolic dimension, LV — left ventricle, IVS — interventricular septum, CRD — conventional renal denervation.

Table 3

Characteristics of antihypertensives' groups used during the follow-up period

	Proportion of use (%)		p
	CRD group	DRD group	
ACE inhibitors	53,0	49,0	0,921
ARBs	47,0	51,0	0,134
CCB	77,6	77,1	0,947
Diuretics	100	100	1,000
Central-acting agents	51,0	42,9	0,513
β-blockers	78,6	66,8	0,079
α-blockers	8,2	6,9	0,476
Direct-acting vasodilators	7,2	6,9	0,391

Abbreviations: DRD — distal renal denervation, ACE — angiotensin-converting enzyme, ARBs — angiotensin II receptor blockers, CCBs — calcium channel blockers, CRD — conventional renal denervation.

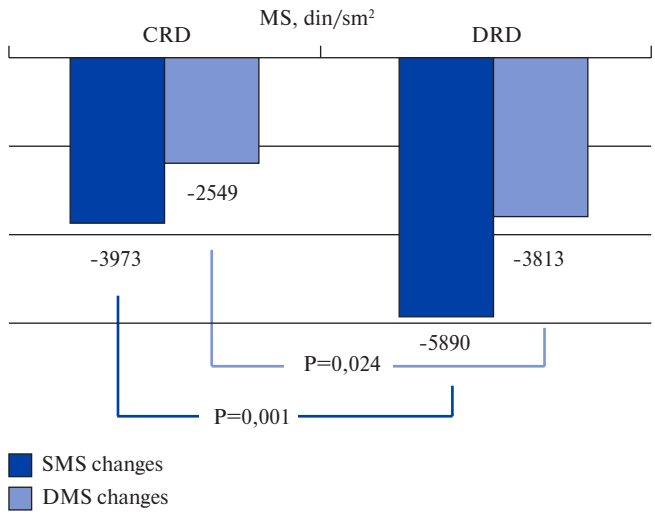

Figure 2. Comparison of changes in MS after CRD and DRD in patients after 12 months.
Abbreviations: DRD — distal renal denervation, DMS — diastolic myocardial stress, MS — myocardial stress, SMS — systolic myocardial stress, CRD — conventional renal denervation.

DRD (Figure 6 B). There was no significant difference between the analyzed techniques in circumferential strain (Figure 6 C).

Discussion

It is well known that studies on RD, especially distal, are still very small in number and samples in them due to some objective reasons: the method has been introduced into clinical practice only in a number of countries and has a rather high cost; new equipment requires licensing by local health authorities and others, but the relevance of research is obvious at the present time [3]. Therefore, the world has a very careful and interested attitude to each clinical trial on RD. To date, some of its cardioprotective effects have been proven in sham-control experimental studies. The researchers noted an increase in LVEF and a decrease in LV end-diastolic volume in models of heart failure, an increase in ventricular diastolic dimension against the background of suppression of LV remodeling substrates (BNP, Ang II, aldosterone, TGF-β expression). A number of clinical studies have also shown a significant decrease in IVS thickness, LV

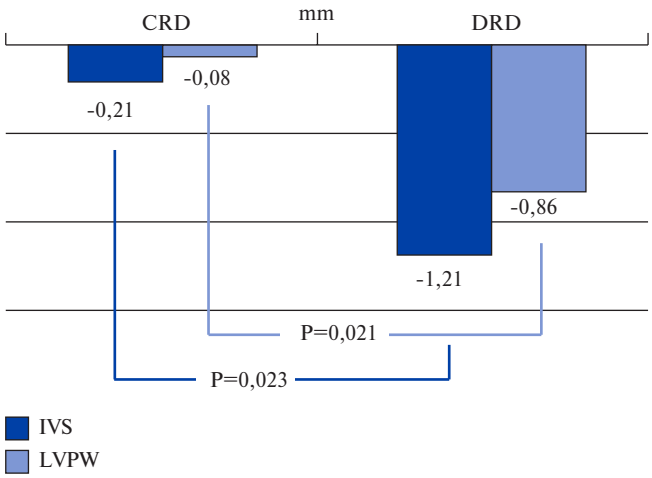

Figure 3. Comparison of changes in LV walls after CRD and DRD in patients after 12 months.
Abbreviations: DRD — distal renal denervation, LVPW — left ventricular posterior wall, IVS — interventricular septum, CRD — conventional renal denervation.

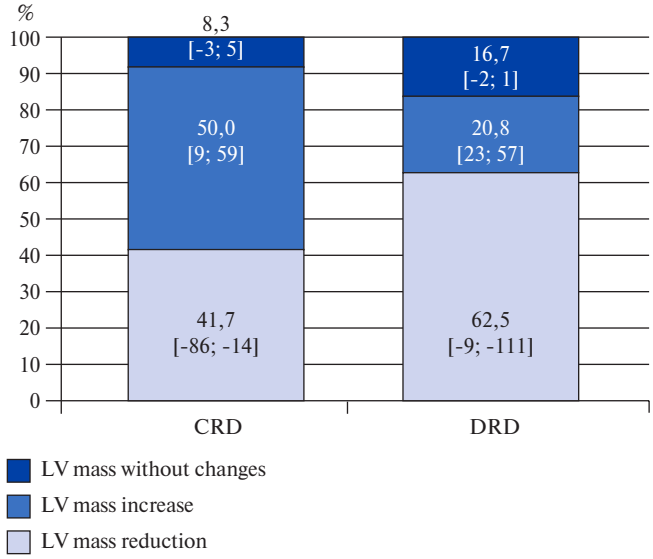

Figure 4. Comparison of changes in LV in the groups after CRD and DRD.
Note: upper figure — intragroup changes presented as %, lower figures — range of changes [min; max].
Abbreviations: DRD — distal renal denervation, LV — left ventricle, CRD — conventional renal denervation.

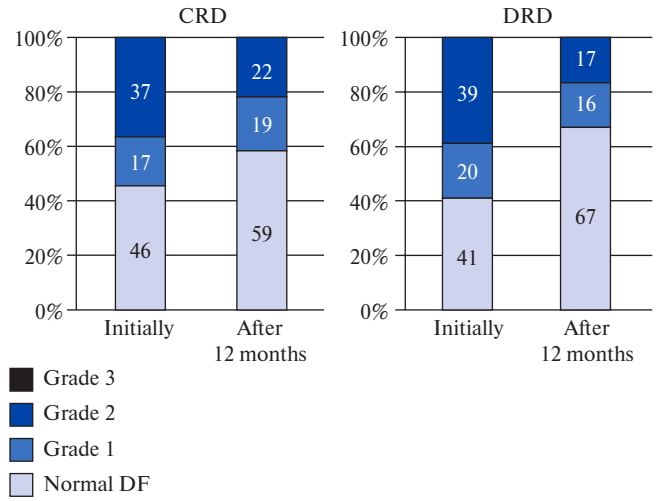

Figure 5. Changes in DD grade and restoration of LV DF after CRD and DRD.
Abbreviations: DRD — distal renal denervation, CRD — conventional renal denervation, DD — diastolic dysfunction, DF — diastolic function.

mass index and normalization of LV DF parameters [7-9]. These data were obtained after CRD. It is very likely that a more targeted effect on the sympathetic nervous system endings in the renal arteries causes a more pronounced antihypertensive effect after DRD. Since in this study, a more pronounced and cardioprotective effect was observed, this may be explained by a decrease in LV wall stress. In addition, a more directed effect on sympathetic nervous system fibers with the afferent response of greater strength should be expected to be realized in the beneficial effects of reducing LV mass But the detailed pathophysiological mechanisms of these processes should still be studied. Our data in 2018-2019 were presented for wide discussion at the congresses on hypertension and cardiology (ESH, ISH, ESC), where one of the frequently asked questions was: why did we not use the LV mass index in our estimations? We would like to give an explanation that this was applied deliberately and reasonably. Since during statistical processing of LV mass index, where each value (IVS, LVPW, end-diastolic size), together with the measurement error, is raised to the third power [10], plus the inspection error of body surface area during follow-up, then, therefore, this significantly increases the total error of calculated LV mass index and, accordingly, requires a much larger number of investigated values to determine the significance of the differences.

Special attention should be paid to the analysis of a pilot study of 2D strain STE parameters for standard LV segments. It is logical to assume that a more pronounced change in the longitudinal and circumferential strain after DRD is associated with a MS change and a decrease in sympathetic nerve activity. At the same time, it is not yet clear why not all LV segments responded equally? Given the small size of sample, of course, this requires further accumulation and verification of data.

Study limitations. The study was single-center, with no comparison to the sham-control group, with a small number of participants and a limited follow-up period.

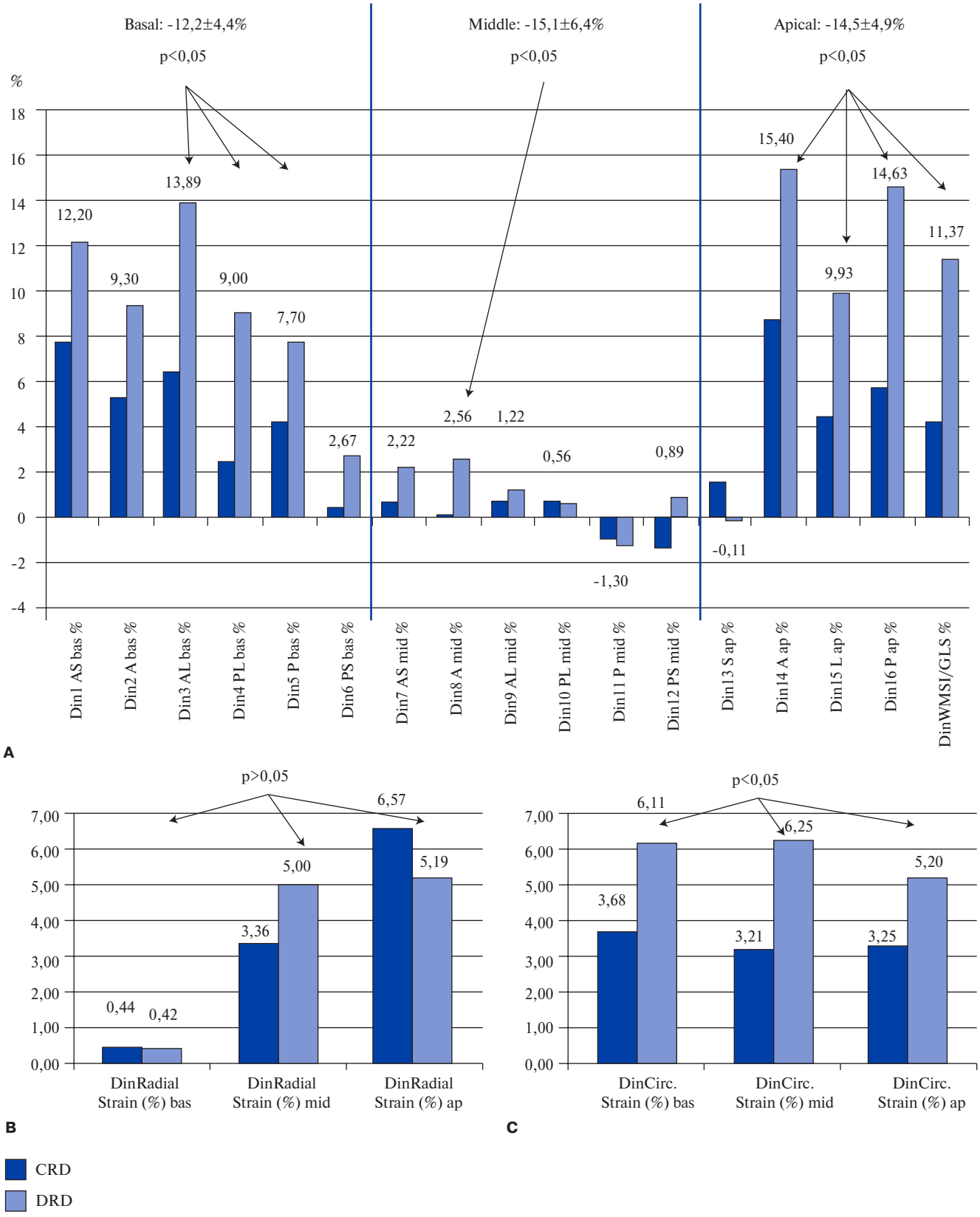

Figure 6. Comparison of changes in LV strain parameters in standard segments 12 months after CRD and DRD: **A** — LV global longitudinal strain, **B** — radial strain, **C** — circumferential strain.
Abbreviations: DRD — distal renal denervation, CRD — conventional renal denervation, A — anterior, AL — anterolateral, ap — apical, AS — anteroseptal, bas — basal, Circ. — circumferential, L — lateral, mid — middle, PL — posterolateral (inferolateral), P — posterior (inferior), PS — posteroseptal (inferoseptal), S — septal, WMSI/GLS — Wall motion score index/Global longitudinal strain.

Conclusion

Twelve months after distal RD, compared with the main renal artery denervation, the LV wall thickness, number of patients with LV hypertrophy, and diastolic dysfunction decreased significantly greater. Two-dimensional STE revealed improvement of cardiac parameters. The results require further research.

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Decreased arterial compliance assessed by aortic pulse wave velocity is an important parameter for monitoring of blood pressure in patients with chronic inflammatory diseases

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Aim. Patients with chronic inflammatory diseases (CID), such as rheumatoid arthritis (RA) and familial Mediterranean fever (FMF) are more likely to have higher risk of cardiac events. Pulse wave velocity (PWV) can be used to measure the aortic distensibility and it is known as inversely related to the arterial compliance. Increased aortic stiffness which is assessed by PWV, is seem to be associated with arterial blood pressure. In this study, we investigated the arterial compliance by PWV in patients with CID including RA and FMF.

Material and methods. We studied 25 patients with RA, 33 patients with FMF and 31 healthy subjects without a history of any cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidaemia (89 subjects in total). We measured the arterial compliance by automatic carotid-femoral (aortic) PWV using Complior Colson (France) device. PWV (m/s) = distance (m)/transit time(s).

Results. It is seen that, patients with CID have higher carotid-femoral (aortic) PWV (8,76±2,09 vs 8,07±0,94 m/s) compared to control groups (p=0,03). There were significant correlations between PWV and age, body-mass index, systolic blood pressure, diastolic blood pressure and mean blood pressure. (p<0,001, r=0,65; p<0,001, r=0,36; p<0,001, r=0,42; p<0,001, r=0,46; p<0,001, r=0,48, respectively).

Conclusion. Arterial compliance, which is assessed by carotid-femoral (aortic) PWV, is decreased in patients with CID such as RA and FMF when it is compared to healthy control group.

Keywords: arterial elasticity, pulse wave velocity, chronic inflammatory disease.

Relationships and Activities: none.

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Chronic immune and inflammatory diseases can present many complex problems for the cardiology, cardiothoracic surgery and anesthesiology practice. Rheumatoid arthritis (RA) and familial Mediterranean fever (FMF) are related with increased risk of cardiac events [1]. Endothelial dysfunction, which is also an early stage of atherosclerotic process, is associated with chronic inflammation [2]. When the arterial wall is damaged due to atherosclerosis, arterial stiffness increases, on the other hand arterial elasticity and compliance decreases [3]. Pulse wave velocity (PWV), inversely correlated with arterial distensibility and relative arterial compliance, is a noninvasive technique that helps to measure and understand such effects on the arterial system [3, 4]. Animal and preoperative studies suggested that PWV as arterial blood pressure changes with different hemodynamic conditions [5]. Increases in arterial blood pressure, heart rate, and systemic vascular resistance were associated with higher values for PWV in cardiothoracic surgical patients [6]. In this study, we investigated the arterial compliance by using PWV, especially in patients with chronic inflammatory diseases (CID), such as RA and FMF.

Material and methods

This cross-sectional study has a total number of 89 subjects including RA (25) who are diagnosed according to 2010 ACR/EULAR Classification Criteria for RA [7] and FMF (33) according to the Simplified FMF diagnosis criteria [8] and healthy subjects (31). All of the patients were inactive during the investigation. We excluded patients with history of previous myocardial infarction, peripheral arterial disease, carotid artery disease, congestive heart failure, renal failure (creatinine of plasma >1,8 mg/dl), arterial hypertension, insulin dependent diabetes mellitus, non-insulin dependent diabetes mellitus, hyperlipidemia, valvular heart disease, atrial fibrillation, anemia (hematocrit <35%), obesity (body-mass index (BMI) >35 kg/m^2 and waist-hip ratio ⩾1). Patients in this study were not treated with beta-blockers, calcium channel blockers, statins, hormone replacement therapy, diuretics, and angiotensin converting enzyme inhibitors, angiotensin receptor blockers and nitrates. The study was carried out in accordance with the standards of good clinical Practice (Good Clinical Practice) and the principles of the Helsinki Declaration. The study Protocol was approved by the Ethical committees of all participating clinical centers. Prior to being included in the study, written informed consent was obtained from all participants.

Measurements. Weight of the patients were measured in kilograms as being in light clothes and without shoes and measurements of their height were taken. BMI (kg/m^2) were calculated dividing body weight in kilograms by square of body height in meters. Waist circumference is measured between the last lib and *crista iliaca* on the midline while the patient was standing. Hip circumference is measured by using the line between right and left trochanter major of femur. The circumference of waist dividing them by circumference of hip, waist-hip ratios were calculated.

Table 1

Basic data and hemodynamic values in control subjects and patients with CID

Parameters	CID	Healthy Group	p
Age (years)	34,5±14,5	37,3±10,8	0,31
BMI (kg/m^2)	24,57±3,99	25,65±3,39	0,18
Waist/Hip	0,83±0,73	0,86±0,08	0,07
SBP (mmHg)	110,26±15,6	115,00±13,10	0,13
DBP (mmHg)	71,38±10,67	72,10±7,61	0,71
MBP (mmHg)	84,34±11,58	86,19±8,07	0,38
Pulse Pressure (mmHg)	38,88±10,13	42,90±11,67	0,11
Heart Rate (beat/min)	78,93±10,30	76,32±9,08	0,22
PWV (m/s)	8,76±2,09	8,07±0,94	0,03

Abbreviations: BMI — body mass index, CID — chronic inflammatory diseases, DBP — diastolic blood pressure, MBP — mean blood pressure, PWV — pulse wave velocity, SBP — systolic blood pressure.

PWV and blood pressure measurements. Systolic (SBP), diastolic (DBP), mean blood pressure (MBP) and pulse pressures were measured in consonant with European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) guidelines [9], using a mercury sphygmomanometer with appropriate cuff sizes, in patients who rest for 20 min (Korotkoff phase I for SBP and V for DBP).

Pulse pressure = SBP — DBP

MBP = [SBP + 2 X DBP] / 3

Arterial elasticity was measured by automatic carotid-femoral (aortic) PWV by using the Complior Colson (France) device; the technical characteristics of this device have been described [4]. PWV of the aorta can be measured by two ultrasounds or strain-gauge transducers (using a TY-306 Fukuda pressure sensitive transducer non-invasively — Fukuda, Tokyo, Japan) that fixed transcutaneously into arteries by a known distance: the right femoral and right common carotid arteries. We repeated the measurements over ten different cardiac cycles, and used the mean value for the final analysis. PWV is calculated with pulse transit time and the distance (between femoral and right common carotid artery

which was measured from the body surface) traveled by the pulse between two recording sites, according to the following formula:
PWV (m/s) = distance (m) / transit time (ms).

Statistical analysis. Statistics were obtained using the ready-to-use program of SPSS version 8.0. All the values were expressed as mean ± standard deviation. The obtained results were assessed by Mann-Whitney U test. Correlations were calculated with the Spearman test. P<0,05 was accepted as statistically significant.

Results

It is seen that, patients with CID have higher carotid-femoral (aortic) PWV (8,76±2,09 vs 8,07±0,94 m/s) compared to control groups (p=0.03) (Table 1). There were significant correlations between PWV and age, BMI, SBP, DBP and MBP (p<0,001, r=0,65; p<0,001, r=0,36; p<0,001, r=0,42; p<0,001, r=0,46; p<0,001, r=0,48, respectively).

Discussion

In this study, arterial compliance assessed by carotid-femoral (aortic) PWV, an indicator of arterial stiffness, is decreased in patients with CID such as RA and FMF, when we compared to the healthy group. Although, the underlying mechanisms of vascular pathologies in patients with CID are not well understood, predominant histopathologic reason is known as vascular inflammation, which is related with endothelial cell injuries [10]. Vascular fibrosis and smooth muscle cell proliferation forms the basis of vascular inflammation, which increases arterial stiffness and decreases arterial compliance. Increased arterial stiffness associated with increased carotid-femoral PWV or decreased arterial compliance may lead left ventricular afterload to increase or myocardial oxygen supply to decrease [10].

RA is an inflammatory and systemic immune disease, which may cause acceleration in atherosclerotic progress and an increase in cardiovascular morbidity and mortality [11]. The mortality of RA patients has remained high even if the standardized mortality ratio of the general population improvements has improved over the years and that might have been the of the most important discoveries over the past twenty years. This inflammation becomes an important factor of the initiation or the progression of atherosclerosis due to impairing endothelial function, arterial compliance and arterial elasticity [12]. Some studies have discovered that RA patients have their arterial elasticity reduced [12, 13].

FMF happens to be an autosomal recessive disorder that has its own ethnicity originating from the Middle East: Sephardic Jews, Armenians, Arabs, Druze and Turks [14]. Recurrent episodes of arthritis, chest/stomach pain, and serosal inflammation mostly along with the fever are the main symptoms of FMF. On the other hand, the main issue with untreated patients is the development of amyloidosis. Inflammation with infiltration by neutrophils is seen in histopathologic examinations. It is shown that arterial elasticity and/or compliance is reduced in patients with FMF [2, 14].

Atherosclerotic cardiovascular disease can be characterized by thickening of the vessel wall. It is possible to come across with atherosclerosis in different stages by non-invasive techniques like carotid-femoral (aortic) PWV and that is important to clinically describe patients under high cardiovascular risks including hypertension, hyperlipidemia, and diabetes mellitus [2, 4]. PWV is inversely proportional to arterial elasticity and relative arterial compliance [4]. Some studies have searched the effects of the different factors on the PWV, such as age, sex, height, weight, inflammatory markers, heart rate and blood pressure [2, 6]. In our study, we observed that the most important factors contributing to increased aortic PWV is age and BMI, because of arterial compliance decreasing caused by decrease in elastin fiber, and increase in collagenous material. Normally, the total elastin and collagen protein levels should be almost the same in all aortic wall parts. Endothelial dysfunction and increased arterial medial calcification cause changes in the extracellular matrix by smooth muscle cell proliferation and increased synthesis of structural proteins including collagen, which are also some of the findings of advanced age [3]. Increased BMI, is traditional cardiovascular risk factors, could be a sign of inactivity and could be associated with inflammation and decreasing arterial distensibility, and/or compliance, as in our study [6]. PWV also depends on blood pressure levels including SBP, DBP and MBP, as in our study, and it decreases at low blood pressure, while increases at high blood pressure [3, 4]. Experimental and preoperative studies demonstrated that PWV as arterial blood pressure changes with different hemodynamic conditions [5, 6]. Increased arterial blood pressure have found with increased PWV in cardiothoracic surgical patients [4].

Study limitations. We took great care to exclude subjects with active RA, FMF and with a history of previous myocardial infarction, diabetes mellitus, hyperlipidemia, heart valve disease, aortic aneurysm, choric renal disease, peripheral arterial disease, cerebrovascular disease. In addition, we are aware that the study could be done with more cases. Therefore, the study will need confirmation in large sample size.

Conclusion

Increased aortic stiffness, measured by PWV while the preoperative anesthetic evaluation, is related with more pronounced hypotension during the induction [1, 15]. Structural changes like smooth muscle hypertrophy, changes of extracellular matrix and increased collagen levels of the vessel wall seems to be cause of reduced arterial elasticity in increased blood [3].

In conclusion, patients with RA, FMF have decreased arterial compliance assessed by carotid-femoral (aortic) PWV — an index of arterial stiffness and a marker of atherosclerosis — when we compared to healthy controls.

Relationships and Activities: none.

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Assessment of prevalence and monitoring of outcomes in patients with heart failure in Russia

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The increasing prevalence of heart failure (HF) serves as a reverse side of the effective treatment for cardiovascular diseases (CVD) and increasing patient survival. Data on the epidemiology of HF and related mortality in Russia are limited. According to the EPOCHA trial (hospital phase), the prevalence of HF in the Russian Federation is 7%. HF can significantly contribute to cardiovascular mortality. However, its recognition is limited by the peculiarities of the mortality coding system in Russia. The article presents the authors' view on the registration of HF-related morbidity and mortality cases and perspectives of using left ventricular ejection fraction <50% for statistical reporting.

Keywords: heart failure, prevalence, morbidity, mortality, left ventricular ejection fraction.

Relationships and Activities: none.

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Heart failure is one of the key contributors to hospitalizations and mortality.

The implementation of a wide range of effective therapies for cardiovascular diseases (CVD) has improved survival and increased life expectancy in patients. The downside of the achieved success is the increased prevalence of heart failure (HF). Among patients with myocardial infarction, especially the elderly ones, there is a decrease in in-hospital mortality, accompanied by an increase in the number of cases of HF [1]. Today HF covers ~60 million people in the world [2] and its prevalence varies significantly — from 0,3% in India to 5,8% in Australia [3]. These proportions can be significantly higher taking into account undiagnosed and unreported cases.

A set of measures in modernization of the healthcare system, in particular, the successful implementation of the Vascular program on emergency care for patients with acute coronary syndrome [4] has led to reduced cardiovascular mortality rate by 36,6% in the Russian Federation (RF) between 2005-2018. Extrapolation of the data of the Russian epidemiological studies EPOCHA-CHF (1998), EPOCHA-Hospital-CHF (2005) and EPOCH-Decompensation-CHF (2015) to the entire population of the Russian Federation demonstrates that from 1998 to 2014 the number of patients with HF of any class increased from 7,19 to 14,9 million cases, and the prevalence of HF — from 4,9 to 10,2% [5]. The greatest growth (from 1,2 to 4,1%) was noted for class III-IV HF. The average prevalence of HF in the Russian Federation is 7% [6], which is significantly higher than in other countries [3]. The duration of the studies, the relatively small sample size, the criteria used to confirm the HF (6-minute walk test and at least one sign on following tests: electrocardiography, chest x-ray, echocardiography [6] emphasize that the data obtained in epidemiological studies on the prevalence of HF in the Russian Federation may not reflect the actual situation.

The presence of HF determines a high risk of adverse outcomes. Despite the treatment using modern drugs and implantable devices, heart failure in terms of progression rate and "malignancy" of the course in many aspects is comparable to the most aggressive types of cancer [7]. Foreign studies indicate a fivefold increase in the death risk in patients with HF [8]. The 1-year survival rate according to a meta-analysis, including 1,5 million patients with any class of HF, averages 87% [9]. About half of patients with heart failure are hospitalized at least once a year, which aggravates the prognosis [10]. The results of early observational studies in the Russian population indicate that the annual mortality rate for any class HF is 6%, and for severe HF — 12% [10]. Decompensated HF is the hospitalization cause for 16,8% of patients with CVD [10], representing a special vulnerable period with the highest risk of adverse events during hospitalization and the next month after discharge. In the large register ORACUL-RF (41 research centers, 20 cities of the Russian Federation), among 2498 hospitalized patients with HF, in-hospital mortality was 9%, 1-month and 1-year mortality after discharge — 13 and 43%, respectively, and rehospitalization rate — 31 and 63,4% [11].

The federal project on the prevention of cardiovascular diseases provides the achievement of the target level of cardiovascular mortality of <450 cases per 100 thousand people by 2024 [12]. This means that in relation to the current level (at the end of 2019, 573,2 cases per 100 thousand people), cardiovascular mortality must be reduced by 21,5% over the next 5 years [4]. The high contribution of HF to the mortality emphasizes the importance of a strategy for the prevention and treatment for HF, which cannot be implemented without regular monitoring of morbidity, mortality and quality control of healthcare specifically in this population.

Prerequisites for the modification of record keeping system for HF patients

Analysis of the cardiovascular mortality patterns in the Russian Federation at the end of 2019 shows that the proportion of acute types is small and amounts to 6,4% for myocardial infarction and 15% for stroke [4]. The dominant cause of death is chronic types of coronary artery disease (46,2%) [4]. It can be assumed that the main contribution to mortality in this subgroup is made by HF, however, data on morbidity and mortality from HF are not published. Some features of CVD coding limit the reporting of HF cases. Since acute and chronic heart failure are severe manifestations of a wide range of cardiovascular or non-cardiac diseases, diseases leading to the HF or associated with it (arrhythmias, sudden cardiac death, pulmonary embolism) are more often taken into account in the structure of morbidity and mortality from CVDs, but not the HF itself. Despite the presence of a I50 code in the International Classification of Diseases of the 10th revision (ICD-10), in most cases, HF is coded as a complication of the underlying disease. Thus, using HF as an indicator of CVD severity and the need for monitoring remains unrealized. The analysis of seeking medical attention in 2018, 2019 and January-November 2020 in St. Petersburg demonstrates that the number of patients with ICD codes of HF or those with its probable presence (I11.0 — hypertensive heart disease with heart failure, I25.5 — ischemic cardiomyopathy, I42.0 —

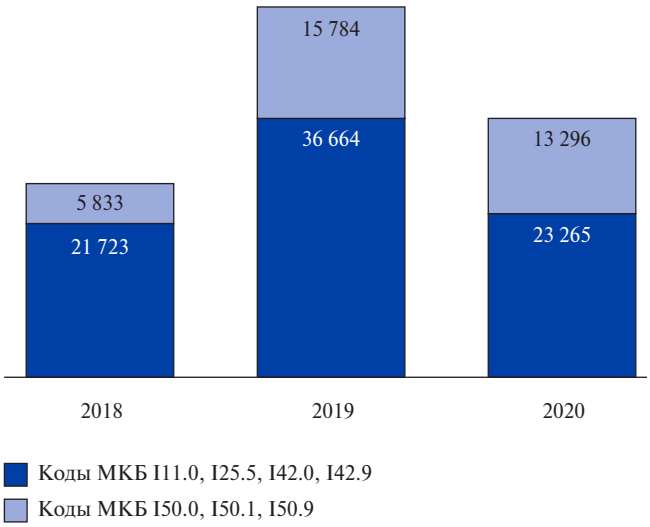

Figure 1. Cases of diseases with ICD codes, potentially including HF (based on data from Chronic Heart Failure registry, which began in 2018 and included individual medical organizations in the pilot phase).
Abbreviation: ICD — International Classification of Diseases.

dilated cardiomyopathy, I42.9 — unspecified cardiomyopathy) significantly exceeds the number of patients with ICD codes that directly encode HF — I50.0, I50.1, I50.9 (Figure 1). Along with this, the mandatory requirement to enter the HF diagnosis code (I50) for all patients with CVD may be associated with a number of organizational problems.

Another factor that complicates the assessment of the real prevalence of HF and associated outcomes is its heterogeneity. In particular, the current criteria for the diagnosis of HF have a number of limitations. The clinical symptoms of HF are nonspecific, the left ventricular ejection fraction (EF) is variable, and the level of natriuretic peptides (NPs) depends on a wide range of concomitant factors that can both underestimate and overestimate the NP values. Taken together, this determines the complexity of identifying and confirming the HF in a particular patient, and, therefore, assessing the prevalence at the population level.

Echocardiography and assessment of left ventricular ejection fraction as a tool in identifying patients with heart failure

Echocardiography is one of the necessary diagnostic methods for patients with CVDs, listed among the criteria for qualitative healthcare, according to the 2020 guidelines on chronic heart failure [9]. The classification criterion for diagnosis and prognostic factor for echocardiography in patients with HF is EF. There are 3 phenotypes of HF, depending on the value of EF — HF with reduced EF (HFrEF <40%), HF with mid-range EF (HFmrEF 40-49%), HF with preserved EF (HFpEF ⩾50%). In the case of symptoms and (or) signs of HF and EF <40%, the diagnosis of HF is beyond doubt. To confirm HFmrEF and HFpEF, additional criteria are required — structural and functional myocardial changes according to echocardiography and an increase in natriuretic peptide. It should be noted that recent studies of the features and effects of drug therapy in HFmrEF indicate the similarity of this phenotype with HFrEF, which may be reason to rename mid-range to mildly reduced EF [13-15], but most importantly, it emphasizes the expected improvement in outcomes in this group, similar to the HFrEF group.

The HFpEF phenotype remains the most controversial in relation to the diagnostic algorithm and management tactics. In patients with unclear dyspnea, the current criteria for HFpEF showed low sensitivity when compared with the gold standard for HF diagnostics — assessment of stress intracardiac hemodynamics [16], and the proposed new scores [17, 18] are not always consistent with each other [19]. Despite the expectedly smaller error in the diagnosis of acute heart failure with preserved EF, analysis of data from a Heart Failure Association EURObservational Research Program Heart Failure Long-Term Registry indicates that HFpEF is confirmed after discharge only in half of the cases [20]. Another unresolved clinical issue is the search for effective proven methods of treatment in this group of HF. To date, none of the drugs studied in numerous randomized clinical trials (RCTs) have shown a beneficial effect on the prognosis in HFpEF [18], and the management of patients with HFpEF is mainly aimed at controlling comorbidities and conditions.

Analysis of the prognostic significance of EF categories according to echocardiography in RCTs and national databases of Australia (NEDA) [21], the USA and England [22] indicates a J-shaped curve of the relationship between all-cause and cardiovascular mortality from EF. In general, outcomes in patients with an EF <50% (especially with an EF <30%) are worse compared to patients with an EF >50%. Although the normal values of EF continue to be discussed, taking into account the threshold EF levels in the current guidelines [10], the most reasonable initial strategy for recording patients with HF and assessing the effectiveness of treatment seems to be the selection and registration of a group of patients with HF with EF <50% (Figure 2). Timely identification of this subgroup and the appointment of drug therapy with proven effectiveness can significantly increase the life expectancy of patients and reduce the risk of hospitalization.

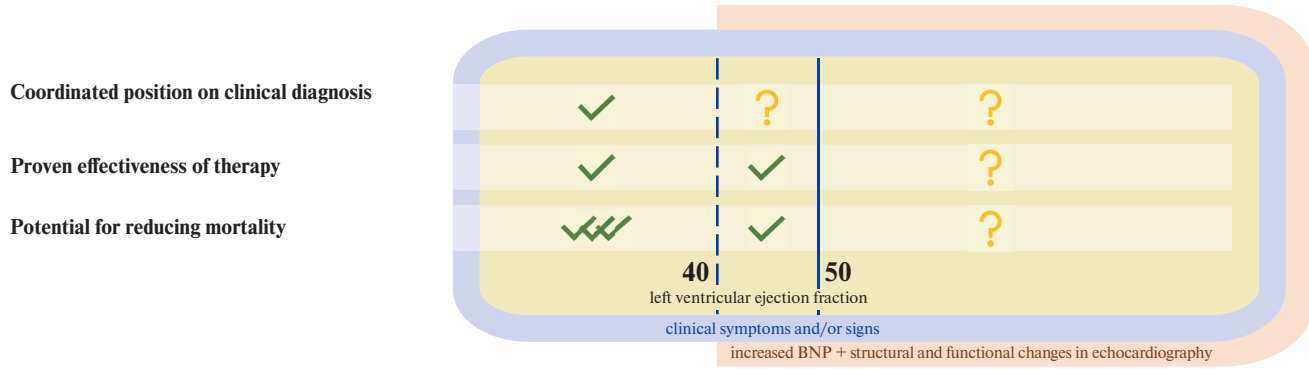

Figure 2. Advantages of the initial strategy for organizing recording system for patients with HF with ejection fraction <50%.
Abbreviation: BNP — brain natriuretic peptide.

Proposed changes in federal statistical survey as the main source of data on morbidity and mortality in the Russian Federation

To take into account the prevalence of HF as a complication of the underlying disease, changes are proposed to the following forms of federal statistical survey and forms of reporting medical documentation (Figure 3):

— Form № 12 (approved by Rosstat order dated November 22, 2019 № 679),

— Form № 14 (approved by Rosstat order dated November 19, 2018 № 679),

— Form № 30 (approved by Rosstat order dated December 30, 2019 № 830),

— Form № 066/u — statistical card of released patient (approved by order of the Ministry of Health of the Russian Federation dated December 30, 2002 № 413),

— Form № 25 — slip of an outpatient receiving medical care (approved by order of the Ministry of Health of the Russian Federation dated December 15, 2014 № 834).

Form № 12 contains information on the number of diseases registered in patients living in the service area of a medical organization, and is one of the main sources of information on the morbidity in the Russian Federation. Data on the prevalence of certain types of CVD are entered in tables (1000, 2000, 3000, 4000). Form № 14 contains information on the activities of departments of a medical organization that provide inpatient health care. Data on the prevalence of certain types of CVD requiring inpatient treatment are entered in the table (2000).

In Forms № 12 and № 14 (tables 1000, 2000, 3000, 4000) it is proposed to add additional columns containing information about EF — "less than 50%", "50% or more" or "not analyzed". These columns are filled in only in patients with the main diagnosis of CvD (ICD-10 I00-I99) and reflect information on the presence of a complication of the main diagnosis in this group of patients. The method for measuring EF is not regulated and it is assumed that it is possible to enter the results of echocardiography or other research methods. Form № 12 contains data on the last value of EF within a year from the date of registration of the disease, while in Form № 14 — on the last value of EF within a year from the moment of discharge from the hospital.

Form № 30 contains information about the medical organization and reflects the number of ultrasound examinations performed annually, including in table 5115 — echocardiography. It is proposed to add additional lines containing information on the number of patients with detected EF <50%, which will allow to indirectly estimate the prevalence of HF in the population. However, a more detailed study is possible only if changes are made to Forms № 12 and № 14.

To implement the presented statistical changes and conduct a thorough control over the reliability of the data entered, it is proposed to amend the following forms of reporting medical documentation:

— Form № 066/u — statistical card of released patient (approved by order of the Ministry of Health of the Russian Federation dated December 30, 2002 № 413),

— Form № 25 — slip of an outpatient receiving medical care (approved by order of the Ministry of Health of the Russian Federation dated December 15, 2014 № 834).

— Form № 066/u contains information about the ICD-10 main diagnosis code for each patient who was in the hospital. Information on the presence of HF and EF can be presented as a separate item requiring completion, or as an additional column in Table 26. It is advisable to provide a choice of 4 options ("50% and more" — 1, "less than 50%" — 2, "not implemented" — 3, "not applicable" — 4). The option "not applicable" is used if the main diagnosis is not related to CVD, while in all other cases one of the first three options should be selected.

(2000)

Наименование болезни	№ строки	Код по МКБ-10 пересмотра	А. Взрослые (18 лет и более)									Фракция выброса левого желудочка при болезнях системы кровообращения I0-I99		
			Выписано пациентов			Проведено выписанными койко-дней	Умерло							
			Всего	из них: доставленных по экстренным показаниям	из них пациентов, доставленных скорой мед. помощью (из гр. 5)		Всего	из них				Более 50%	Менее 50%	Не анализировалась
								проведено патолого-анатомических вскрытий	из них установлено расхождений диагнозов	проведено судебно-медицинских вскрытий	из них установлено расхождений диагнозов			
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
хронический отит	9.1.2	H65 2-4, H66 1-3										X	X	X
болезни слуховой (евстахиевой) трубы	9.1.3	H68 - H69										X	X	X
перфорация барабанной перепонки	9.1.4	H72										X	X	X
другие болезни среднего уха и сосцевидного отростка	9.1.5	H74										X	X	X
болезни внутреннего уха	9.2	H80, H81, H83										X	X	X
из них: отосклероз	9 2 1	H80					X	X	X	X	X	X	X	X
болезнь Меньера	9 2 2	H81.0										X	X	X
кондуктивная и нейросенсорная потеря слуха	9.3	H90					X	X	X	X	X	X	X	X
из них: кондуктивная потеря слуха двусторонняя	9.3.1	H90.0					X	X	X	X	X	X	X	X
нейросенсорная потеря слуха двусторонняя	9.3 2	H90 3					X	X	X	X	X	X	X	X
болезни системы кровообращения	**10.0**	**I00 - I99**												
из них: острая ревматическая лихорадка	10.1	I00 - I02												
хронические ревматические болезни сердца	10 2	I05 - I09												
из них: ревматические поражения клапанов	10 2.1	I05 - I08												
болезни, характеризующиеся повышенным кровяным давлением	10.3	I10 - I13												
из них: эссенциальная гипертензия	10.3.1	I10												
гипертензивная болезнь сердца (гипертоническая болезнь с преимущественным поражением сердца)	10.3.2	I11												
гипертензивная болезнь почек (гипертоническая болезнь с преимущественным поражением почек)	10.3.3	I12												
гипертензивная болезнь сердца и почек (гипертоническая болезнь с преимущественным поражением сердца и почек)	10.3.4	I13												
ишемические болезни сердца	10 4	I20 - I25												
из них: стенокардия	10 4 1	I20												
из нее: нестабильная стенокардия	10 4.1.1	I20.0												
острый инфаркт миокарда	10 4 2	I21												
повторный инфаркт миокарда	10 4.3	I22												
другие формы острых ишемических болезней сердца	10.4 4	I24												
хроническая ишемическая болезнь сердца	10 4 5	I25												
из нее постинфарктный кардиосклероз	10.4.5.1	I25.8												

Figure 3. An example of changes proposed to Form № 14.
Abbreviation: ICD — International Classification of Diseases.

Table 1

Signal indicators for monitoring the system of medical care for heart failure

№	Parameter	Estimation of method, unit of measure	Target value	Explanation
1	Proportion of registered CVD cases with ejection fraction <50% of all CVD cases in the subject of the Russian Federation	Number of identified patients with CVD with EF <50% among all registered patients with CVD in the current year, %	Will be figured out after receiving primary data	Reflects the contribution of the highest risk heart failure to the structure of CVD morbidity — with reduced EF (EF <50% is a predictor of unfavorable outcomes)
2	Prevalence of CVDs with EF <50%	Number of registered patients with CVD with EF <50%, per 100 thousand population at the beginning of the analyzed period	Will be figured out after receiving primary data	Reflects the primary and general incidence of CVD with EF <50%, and indirectly — the effectiveness of primary and secondary prevention in groups of high and very high cardiovascular risk
3	Proportion of patients who died from CVDs with EF <50% of all deaths from CVDs in the subject of the Russian Federation	The death rate from CVD with EF <50% in the current year, of all registered deaths from CVDs, %	Will be figured out after receiving primary data	Reflects the contribution to the structure of mortality from CVDs of the CVD cohort with EF <50% (highest risk groups)
4	Reduction of mortality from CVD with EF <50%	Change in the number of deaths from CVDs with EF <50% in the current year (compared to the previous year/same period of the last year), from all registered deaths from CVDs with EF <50%, %	Decrease no less than 1% compared to the previous year/ same period last year	Shows the effectiveness of the organization of healthcare system and dispensary monitoring of patients with CVDs with EF <50% (highest risk groups)
5	Proportion of in-hospital deaths from CVD with EF <50% of all in-hospital deaths from CVDs	Number of in-hospital deaths from CVDs with EF <50%, of all registered in-hospital deaths from CVDs, %	Will be figured out after receiving primary data	Demonstrates the contribution of mortality in a cohort of CVD patients with EF <50% (highest risk group) to in-hospital mortality from CVDs in general
6	Reduction of in-hospital mortality in patients with CVDs with EF <50%	Change in the number of patients with CVDs with EF <50% who died in the hospital in the current year, from all hospitalized patients with CVDs with EF <50% compared to the previous year/same period of the last year, %	Decrease no less than 5% compared to the previous year/same period of the last year, correction is necessary after obtaining the baseline value	A complex indicator reflecting the effectiveness of both inpatient and indirectly outpatient (late admission, late hospitalization, therapy ineffectiveness) stages of healthcare for patients with CVDs with EF <50% (highest risk groups)
7	Proportion of patients with CVDs with ejection fraction <50% under dispensary monitoring	Proportion of people with CVDs with EF <50%, who are under dispensary monitoring, who received medical services in the current year as part of dispensary monitoring, of all patients with CVDs with EF <50%, who are under dispensary monitoring, %	No less than 80%	Reflects the effectiveness of the outpatient care to patients with CVDs in terms of coverage of dispensary monitoring of patients in the CVD group with EF <50% (highest risk), as well as the continuity of inpatient and outpatient stages of treatment
8	Influenza vaccination coverage of CVD patients with ejection fraction <50%	Proportion of people with CVDs with EF <50% who received influenza vaccination in the current year, from all patients with CVDs with EF <50%, %	No less than 50%	Reflects the effectiveness of the outpatient care to patients with CVDs in terms of the implementation of preventive measures on outcomes in a cohort of CVD patients with EF <50% (highest risk)
9	Pneumococcal vaccination in patients with CVDs with ejection fraction <50%	Proportion of people with CVDs with EF <50% who received pneumococcal vaccination in the previous 5 years or in the current year, from all patients with CVDs with EF <50%, %	No less than 50%	Reflects the effectiveness of the outpatient care to patients with CVDs in terms of the implementation of preventive measures on outcomes in a cohort of patients with CVDs with EF <50% (highest risk)

Abbreviations: CVD — cardiovascular disease, RF — Russian Federation, EF — ejection fraction.

— Form № 25 contains information on the ICD-10 final diagnosis code of each outpatient. It is advisable to provide information on the presence of HF as an additional item to be filled out. For example, immediately after information about the nature of the injury, there may be information about EF in patients with CVDs (ICD-10 I00-I99). In this case, the choice from the previously described 4 coding options is also discussed.

The introduction of the presented changes (Form № 066/u and Form № 25) will allow the formation of measures for independent control over the quality of entering statistical data, and will also provide tools for the quick and correct collection of the necessary information about HF. This will allow the services of the territorial fund of compulsory medical insurance to conduct independent accounting and control of HF prevalence in the region. Isolated changes in the forms of federal statistical survey without the formation of available tools for collecting the required information can lead to the receipt of distorted data.

Monitoring the prevalence and outcomes in patients with heart failure

Isolation and registration of groups of patients with CVDs and EF <50% provides an opportunity to assess the prevalence of HF with reduced and mid-range EF (<50%) in each subject of the Russian Federation and use these data to calculate indicators characterizing the system of healthcare for this category of patients.

Despite prescribing effective drugs for the survival of high-risk patients is the main strategy for reducing cardiovascular mortality, and HF in particular, the assessment of the quality of drug therapy by the frequency of use of recommended drug classes and the percentage of achieving target doses is limited by the need registration of personal data of patients (hemodynamic status, renal function, comorbidities, contraindications), currently unavailable. Similar restrictions apply to the recording of the number of performed high-tech treatments for HF, since they are recommended for patients with a life expectancy of more than 1 year with persistence of HF symptoms while taking maximum tolerated doses of drugs for 3 months. Accounting for these parameters requires an expert assessment.

At the initial stage, monitoring of the indicators listed in Table 1 is proposed as signal indicators for assessing the system of healthcare for HF.

Assessment of the mortality rate in patients with CVDs and ejection fraction <50% in a specific medical institution and at the regional level may reflect the possibilities and effectiveness of the use of drug therapy and mechanical circulatory support, extracorporeal membrane oxygenation, renal replacement therapy, multidisciplinary team work with the involvement of related specialists for determining tactics in non-standard and difficult cases.

An effective system for the identification and long-term follow-up of patients with HF in primary care institutions, including the implementation of seamless management with continuity of healthcare between inpatient and outpatient stages, timely identification of patients with HF and admission to dispensary observation, are of decisive importance in strategies to reduce mortality [23, 24]. The implementation of a similar model in the Russian Federation, compared with standard management, was associated with a 21,2% reduction in 2-year all-cause mortality risk [25]. Vaccination programs require active attention, including educational work with patients. The results of actual clinical practice and observational studies indicate the possibility of reducing the risk of all-cause death by 20% due to influenza and pneumococcal vaccination in patients with HF. In Denmark (n=134048), annual influenza vaccination of patients with HF was accompanied by a 19% reduction in the risk of death [26]. The results of a meta-analysis of 7 observational studies (n=163756) indicate that pneumococcal vaccines are associated with a 22% reduction in the death risk in patients with CVD, including HF, or with a very high risk of their development. Currently, RCTs are being conducted to assess the severity of the effect of influenza and pneumococcal vaccination [27]. However, the available data made it possible to include these strategies in the European and American guidelines for the diagnosis and treatment of HF. According to Russian guidelines, influenza and pneumococcal vaccination is recommended for all patients with HF (in the absence of contraindications) to reduce the risk of death [10].

Conclusion

Data on the epidemiology of HF in the Russian Federation are limited. The increase in the prevalence and potential contribution of HF to mortality pattern emphasize the social and economic significance of the problem, the monitoring of which is not possible without creating a current epidemiological picture by recording and collecting official statistical information. The cumulative assessment of HF prevalence (ICD-10 coding and EF <50%), as well as the calculation of integral indicators characterizing the healthcare system at all stages is a promising direction for implementation of the federal project on the prevention of cardiovascular diseases and control of achieved targets.

Relationships and Activities: none.

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Diagnostic significance of complete blood count in cardiovascular patients

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This article discusses the relationship between parameters of complete blood count (CBC) and cardiovascular diseases (CVD). The main advantages of CBC over other methods of CVD diagnostics are low cost and wide availability. At the same time, the low specificity of CBC is an important disadvantage, limiting its diagnostic value.
After analyzing the results of numerous clinical studies, we concluded that the most important CBC are red cell distribution width, mean platelet volume, total leukocyte count, neutrophil to lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte to high-density lipoprotein ratio. We discuss the diagnostic value of each of the above indicators in CVD. Careful attention to these parameters by clinicians can, to a certain extent, improve the therapeutic and diagnostic process in patients with CVD.

Keywords: complete blood count, cardiovascular diseases, red cell distribution width, mean platelet volume, leukocytes, neutrophil to lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte to high-density lipoprotein ratio.

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Cardiovascular diseases (CVD) are globally characterized by widespread prevalence, high mortality, and disability rate [1-3]. CVDs are usually diagnosed via a clinical examination using relatively expensive methods: functional diagnostics, immunochemical methods determining cardiac biomarkers, such as natriuretic peptides, cardiac troponins, etc. [1, 4]. Along with clinical laboratory and systematic functional studies, doctors also widely use clinical blood testing to assess patients' conditions. Such a test is low in cost and widely available, which provides a suitable approach to analyzing and diagnosing problems such as anemia, the risk of infection and/or hematological malignant neoplasms, inflammatory diseases, and coagulation disorders [5, 6]. However, due to its low specificity for CVD diagnosis, the blood test parameters are sometimes overlooked.

Nowadays, with the improvement of present-day advancements and the presence of programmed hematology counters (automated hematology analyzers), it is possible to measure particular parameters associated with changes in the shape and size of cells, in addition to an accurate quantitative study of blood cells, which makes it possible to calculate several additional indicators using software formulas [7, 8]. These calculated values can facilitate the diagnosis and monitoring of many diseases, including CVD. In this review, based on many foreign studies, we estimate the relationship between some modern clinical blood test parameters to CVD and discuss the possibility of their use to monitor CVD and determine patients' prognosis.

According to current data from international research, the most significant diagnostic/prognostic values among all clinical blood test parameters concerning CVD are the following: red cell distribution width (RDW), mean platelet volume (MPV), total white blood cell count (WBC), neutrophil-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte to high-density lipoprotein ratio (MHR). We considered each of these indicators' diagnostic value and discussed the possible mechanisms underlying the change in reference values.

RDW as an independent predictive biomarker for CVD

RDW is an indicator of the clinical blood test, which makes it possible to characterize the degree of variability in size (volume) of erythrocytes — *anisocytosis* (from the Greek *anisos* — 'unequal', *cytos* — 'cell') [9, 10]. Modern hematology analyzers can calculate RDW and detect anisocytosis much faster and more accurately than the microscopic examination of a blood smear. Normal RDW values are 11,5-14,5% but may vary slightly depending on the type of analyzer. This indicator is commonly used for the differential diagnosis of various types of anemias. There are three types of anisocytosis (increased RDW): anisocytosis due to microcytes (small erythrocytes) — characteristic of iron deficiency anemia; anisocytosis due to macrocytes (large erythrocytes) — observed in megaloblastic anemia and mixed anisocytosis — occurs in newborns (physiological anisocytosis) [11, 12].

Several types of research have mentioned the role of RDW as an independent predictive biomarker in cardiovascular diseases. In particular, it was noted that increased RDW is associated with adverse outcomes and mortality in patients with arterial hypertension, heart failure, stroke, acute myocardial infarction (MI), peripheral arterial disease, and in patients with a history of primary coronary intervention. This relationship can be traced in many studies [13-15]. Nevertheless, the specific pathophysiological mechanisms linking increased RDW to CVD are not completely clear [9, 16]. There are several hypotheses and assumptions about this. Systemic factors such as inflammation increased neuroendocrine system activity, and oxidative stress is the most likely hypothesis to explain the relationship between increased RDW and cardiovascular diseases. Mechanisms such as inflammation, increased activity of adrenergic mechanisms, and the renin-angiotensin-aldosterone system, which are frequent CVD companions, lead to a change in the maturation of erythrocyte precursors and a change in the size of erythrocytes — anisocytosis and an increase in RDW. Oxidative stress also significantly increases RDW in acute inflammatory conditions, causing damage to erythrocyte cell membranes and enhancing the release of immature erythrocytes from the red bone marrow into peripheral blood [10, 12, 16].

A prospective cohort study of 696 adult patients with congenital heart disease (Boston Biobank of Congenital Heart Diseases) discovered a correlation between increased RDW and poor outcomes. The average RDW was 14,0±1,3%. In 81 patients (11,6%), the RDW value exceeded the 15% mark. Mortality among patients with RDW >15% was on average 4,5 times higher than in the rest of the study participants (odds ratio (OR) 4,5 (95% confidence interval (CI) (3,0-6,6)) , p<0,0001) [17].

The diagnostic value of the erythrocyte parameter RDW in CVD has been confirmed in many studies with a relatively large number of examined patients. Almost identical results were obtained across all studies, which support a link between increased RDW and poor CVD outcomes. Also, a decreased RDW has been associated with a favorable prognosis

Table 1

CVD-Associated clinical blood test markers from Clinical Trials

Parameter of the clinical blood test	Diagnosis, number of patients	Clinical data, statistical indicators	Source
RDW	Diabetes (n=3061)	RDW proved to be a significant and independent predictor of death from all causes in these patients	S. Al-Kindi (2017) [13]
	Acute MI, Heart failure, stroke (n=26784)	RDW is associated with the rate of primary hospitalization	Y. Borne (2011) [15]
	Congenital heart disease, congestive heart failure (n=696)	Elevated RDW is an independent predictor of all-cause death in adult patients with chronic heart failure	L. Alshawabkeh (2018) [17]
	Acute heart failure (n=1702)	High RDW was correlated with an increased risk of anemia in patients with acute heart failure	J. Nunez (2011) [27]
MPV	Patients with various diseases (n=206554)	Increased MPV is correlated with a higher risk of death in patients with coronary artery disease	G. Slavka (2011) [28]
	Patients without special conditions (n=25923)	Increased MPV is a predictor of venous thromboembolism	S. Braekkan (2010) [22]
	Patients with venous thromboembolism (n=594)	High MPV is an independent risk factor for death in venous thromboembolism	J. Díaz (2019) [24]
	Patients with acute pulmonary embolism (n=192)	MPV is associated with right ventricular dysfunction and is an independent predictor of early death in acute pulmonary embolism.	M. Kostrubiec (2010) [25]
	Patients with stable coronary artery disease (n=2872)	Low MPV was associated with worse clinical outcomes in patients	H. Wada (2018) [29]
	Portal vein thrombosis (n=855)	As a prognostic biomarker, MPV can be used in patients with portal vein thrombosis	W. Lin (2018) [30]
WBC	Senile patients (73-91) without ischemic heart disease (n=2879)	Increased WBC is associated with a higher risk of congestive heart failure	S. Karino (2015) [32]
	Acute MI (n=975)	Increased WBC is associated with decreased blood flow and higher death rates from new congestive heart failure	H. Barron (2000) [33]
	Ischemic heart disease, ischemic stroke (n=13555)	An increase in WBC is directly related to an increase in CVD mortality (p<0,001)	C. Lee (2001) [37]
NLR	PAOD (n=508)	Higher NLR Associated with Higher CVD Mortality	M. Erturk (2014) [39]
	Acute coronary syndrome (n=400)	Elevated NLR is associated with higher all-cause mortality	Bajari R. (2017) [40]
PLR	MI without ST-segment elevation (n=619)	Higher PLR is a significant independent indicator of long-term patient mortality (p<0,0001)	B. Azab (2012) [46]
	PAOD (n=2121)	Increased PLR is significantly associated with critical limb ischemia in patients at higher risk of CVD endpoints (optimal PLR threshold is 150) (p<0,001)	T. Gary (2013) [47]
MHR	ST-segment elevation MI (n=414)	MHR is an independent predictor of high thrombotic load in patients with ST-segment elevation MI (p<0,001)	A. Arısoy (2017) [43]
	Obstructive sleep apnea syndrome with and without various CVDs (n=1050)	MHR values are significantly higher in patients with CVD compared with patients without CVD (p<0,001)	H. Inonu Koseoglu, et al. [48]

Abbreviations: IHD — Ischemic heart disease, MI — myocardial infarction, CBC — clinical blood test, AMI — acute myocardial infarction, HF — heart failure, CVD — cardiovascular diseases, MHR — monocyte to high-density lipoprotein ratio, MPV — mean platelet volume, NLR — neutrophil-lymphocyte ratio, PAOD — peripheral arterial occlusive disease, PLR — platelet-to-lymphocyte ratio, RDW — red cell distribution width, WBC — total white blood cell count.

in cardiac patients. Thus, a recent meta-analysis by Abrahan L, et al. (2018), which included 13 studies and 10410 patients, showed that a lower level of RDW is associated with a decrease in the risk of adverse cardiovascular events in patients with the acute coronary syndrome (OR 0,35 (95% CI 0,30 to 0,40), p<0,0001; I^2=53%) both in the short and long term [18]. Several studies have also demonstrated the role of RDW levels in predicting the growth of atherosclerotic plaque of the carotid artery and the relationship between acute heart failure and increased RDW [16, 19]. Red cell distribution width indicator can be considered a valuable independent biomarker for assessing patients' prognosis with heart failure, atherosclerosis, acute MI, and other CVDs.

MPV as an independent risk factor (RF) for CVD

Platelets perform a vital function — they prevent bleeding by forming a thrombus at the site of vascular damage, but their inadequate functioning leads to thrombosis and, as a result, to ischemia of the corresponding tissues and organs. There is a direct relationship between the size of platelets and their activity. Platelet activity can be indirectly measured using MPV (a parameter measuring the size of circulating platelets) [20, 21]. The normal MPV value is from 7 to 10 fL, depending on the type of analyzer and its operating principles. Various studies have found a correlation between an increase in MPV and CVD and noted a predictive role for this biomarker in these diseases. For example, an increase in MPV is associated with acute MI, unstable angina, and stroke. An increase in platelet volume is also associated with an increased risk of death caused by CVD [21, 22]. Another study demonstrated that MPV is the risk factor for unprovoked venous thromboembolism, suggesting that MPV and platelet activity are risk factors for developing arterial and venous thrombosis [23]. In a recent retrospective study, Díaz J, et al. it was found that a high level of MPV (>11,0 fL) is an independent risk factor of death in patients with venous thromboembolism [24]. Kostrubiec M, et al. also reported that elevated MPV levels (>10,9 fL) are independent predictors of early mortality in patients with acute pulmonary embolism during first 7 and 30 days: OR =2,0 (95% CI 1,3-3,0), p<0,001 and OR =1,7 (95% CI 1,2-2,5), p<0,01, respectively. In addition, a correlation was found between MPV and right ventricular diameter (r=0,28, p<0,01), as well as between MPV and right ventricular dysfunction (r=0,19, p<0,02) [25].

Current studies have shown a strong correlation between platelet size and platelet activity, which explains the pathophysiological mechanisms of the relationship between MPV and CVD. Larger platelets are more active than smaller platelets; they also have more storage granules and have a higher capacity to produce prothrombogenic factors such as thromboxane A2. It is believed that MPV increases in CVD due to tissue ischemia, platelet consumption in atherosclerotic plaques, and secretion of cytokines — Interleukin-3 (IL-3) and Interleukin-6 (IL-6), which affect the ploidy of megakaryocytes. IL-3 and IL-6 increase the size and deformation of platelets and promote the release of larger and more active platelets [21, 26], causing additional adhesion and aggregation of platelets through the release of thromboxane A2, adenosine diphosphate (ADP), and adenosine triphosphate (ATP), contributing to the pathogenesis of CVD acute MI [27]. Considering the rapid increase in MPV during the first hours of acute CVD development and its persistence in elevated values for several days after CVD development, this RF can be used as a prognostic/diagnostic biomarker for CVD, especially acute MI and ischemic stroke. The rapidity and stability of the MPV increase are the main advantages of this essential diagnostic/prognostic parameter [28-30].

Inflammatory markers that can predict adverse cardiovascular events

Generally, an increase in total white blood cell count (WBC) and an imbalance in the leukocyte formula, expressed as an increase in the percentage of neutrophils and a decrease in lymphocytes, are considered the main laboratory signs of inflammation [31, 32].

Several studies have established a link between inflammation and CVD markers and showed that inflammatory processes play a decisive role in the pathogenesis of atherosclerosis, which predisposes to most CVDs [33, 34]. Hence, measurement and evaluation of inflammation markers play a critical role in determining patients' prognosis with CVD [35].

Neutrophil-lymphocyte ratio (NLR) is an inflammatory marker that can predict the likelihood of death in patients with acute coronary syndrome and arrhythmias. Normal NLR value should not exceed 3.0. An increase in this ratio is associated with an increased risk of CVD and mortality rates from all causes, including congestive heart failure [36]. It has been shown that with NLR >3,15, the risk of atrial fibrillation in patients increases 2,5 times. NLR is an important marker for assessing the prognosis of patients with CVD because it is minimally influenced by physiological conditions of the patient, as a result of which it provides an opportunity to check the balance or imbalance of the immune pathways of inflammation (the number of neutrophils), as well as the body's response to

stress (the number of lymphocytes) [36, 37]. One of the hypotheses of the relative mechanism of an increase in the NLR ratio is a decrease in the number of lymphocytes after programmed cell death (apoptosis) or the movement of lymphocytes from peripheral blood into cardiac tissue followed by its infiltration, which was found in patients with heart failure and acute MI [31]. An increase in NLR is often accompanied by an increase in neutrophils and total leukocyte count, which is also the risk factor of atherosclerosis. Elevation of these parameters is associated with a higher incidence of ischemic heart disease (IHD) and ischemic stroke, since neutrophils and macrophages increase phagocytosis and degradation of vascular tissue and, as a consequence, the progression of atherosclerosis — the growth of atherosclerotic plaque followed by vascular occlusion [38-40]. An increase in total WBC is also associated with decreased blood flow to cardiac tissue [33].

Several studies have shown that inflammation is closely related to lipid metabolism. The total number of leukocytes and numbers of individual subpopulations (neutrophils and lymphocytes) are associated with the concentration of a relatively recently discovered regulator of lipid metabolism — Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) [41-43]. In patients with myocardial infarction (MI) without ST elevation, PCSK9 concentrations were elevated on admission and were associated with neutrophil count (r=0,24; p=0,009). The anti-inflammatory drug tocilizumab, containing the monoclonal antibodies of the cytokine IL-6, reduced both the concentration of leukocytes and the concentration of PCSK9. Presumably, leukocytes, releasing pro-inflammatory factors, increase the formation of PCSK9, which is another additional pathophysiological mechanism of atherosclerosis progression [41, 43].

In a study by Li S, et al. (2014) the relationship between plasma levels of PCSK9 and WBC (r=0,167; p=0,008) were noted in patients with stable coronary artery disease (n=251). Multivariate regression analysis discovered that plasma PCSK9 concentration was significantly and independently associated with WBC and their subpopulations (neutrophils and lymphocytes). Researchers believe that PCSK9 is involved in developing chronic atherosclerotic inflammation in the walls of coronary arteries and promoting coronary artery disease [42].

MHR can also be considered a valuable indicator retrieved from clinical and biochemical blood tests. A massive study by Zhang Y, et al. (2016) showed that MHR is an independent marker of major adverse cardiovascular events, including death, acute MI, heart failure, unstable angina, and stroke. This is because high-density lipoproteins (HDL) play an antiatherogenic and anti-inflammatory role by inhibiting CD11b integrin activation, which is involved in the adhesion migration and regulation of the inflammatory activity of monocytes/macrophages [34]. Consequently, an increase in the MHR ratio, characterized by an increase in the number of monocytes and/or a decrease in HDL, indicates inhibition of the protective anti-inflammatory and antiatherogenic mechanisms.

Arisoy A, et al. (2017) assessed the relationship of MHR with angiographic thrombotic load calculated on the basis of thrombolysis in patients with ST-segment elevation MI (STEMI) who underwent primary percutaneous coronary intervention (n=414). In patients with a high thrombotic load, the MHR index was significantly higher than in patients with a low thrombotic load (25,4 (13,5-44,6) vs. 16,0 (9,2-22,1); p<0,001) [44]. Thus, the MHR index is an independent predictor of high thrombotic load in patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention.

Similar to the ratios of NLR and MHR, platelet-to-lymphocyte ratio (PLR) is another marker of inflammation with a significant predictive value. An increase in it correlates with increased functional activity, platelet count, decreased lymphocyte count, and a poor prognosis in patients with CVD [45]. A study by Azab B, et al. (2012) found that PLR is a significant independent predictor of long-term (4-year) mortality after MI [46]. Interestingly, mortality at a PLR value of >176 in patients treated with one antiplatelet drug was significantly higher than in patients receiving dual antiplatelet therapy: 50% vs. 32%, p=0,0018 [46].

In another clinical study with Gary T, et al. (2013) investigated the PLR value in patients (n=2121) with the peripheral arterial occlusive disease (PAOD). The optimal PLR value was 150 or less, and patients with PLR >150 developed critical limb ischemia much more often (OR 1,9 (95% CI 1,7-2,1)). An increase in PLR was associated with critical limb ischemia even after adjusting for all other well-known CVD risk factors [47].

Clinical blood test parameters and clinical application

Table 1 summarizes the clinical studies results that showed the relationship between clinical blood test parameters and various CVD parameters. It is worth noting that the clinical blood test parameters' exact reference values may differ depending on the type of analyzer, its principles of operation, and units of measurement. Therefore, we avoided excessive use of specific numerical indicators when analyzing individual clinical studies. Specific hospitals

should make empirical (experimental) estimates, particularly on retrospective patient data, for the optimum use of the clinical blood test for tracking and predicting CVD.

Conclusion

The diagnostic/prognostic value of clinical blood test parameters for CVD is an important research area. Clinical blood testing is an inexpensive, widespread, and at the same time, a valuable additional prognostic tool for patients with CVD.

After analyzing the results of clinical studies, we concluded that such blood testing parameters as red cell distribution width, the mean platelet volume, the total white blood cell count, the neutrophil-lymphocyte ratio, the platelet-to-lymphocyte ratio, the monocyte to high-density lipoprotein ratio are reliable in monitoring and assessing the prognosis of various cardiovascular diseases. Such diseases include atherosclerosis, MI, stroke, heart failure, venous thromboembolism, and PAOD. These parameters represent the most accessible and easy-to-use tools for assessing the prognosis of patients' life, which is their undoubted advantage over complicated, expensive, and time-consuming examination methods. Further research is required in this area, both of a fundamental (the study of specific pathophysiological mechanisms) and clinical types, to study the possibilities of widespread use of these indicators in real clinical practice.

Relationships and Activities: none.

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