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IN ISSUE:

Novel diagnostic criteria for atrial cardiomyopathy in patients with type 2 diabetes and atrial fibrillation

Glycemia in patients with type 2 diabetes during inpatient treatment for acute myocardial infarction: impact on prognosis

Carbohydrate metabolism disorders in patients with heart failure: data from the local registry

Early diagnosis of myocardial fibrosis in patients with epicardial obesity

Biomarkers of inflammation, parameters characterizing obesity and cardiac remodeling in patients with atrial fibrillation and metabolic syndrome

International register “Dynamics analysis of comorbidities in SARS-CoV-2 survivors” (AKTIV) and the register "Analysis of hospitalizations of comorbid patients infected during the second wave of SARS-CoV-2 outbreak" (AKTIV 2)

IN FOCUS:
Diabetes, Metabolic syndrome

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International register “Dynamics analysis of comorbidities in SARS-CoV-2 survivors” (AKTIV) and the register “Analysis of hospitalizations of comorbid patients infected during the second wave of SARS-CoV-2 outbreak” (AKTIV 2)

Dear readers, the new issue of the Russian Journal of Cardiology dedicated to the most important problem of modern cardiology — cardiometabolic syndrome.

The complexity of its treatment and absence of success in reducing its prevalence set us the task of further studying the multifaceted clinical manifest of a severe pathological condition.

In recent years, there has been great interest in the study of diabetes, obesity and related cardiovascular and metabolic complications. In this regard, comorbidities and modern trends in the management of care, which can significantly reduce cardiovascular and all-cause mortality, are given special attention. The journal presents the results of original studies on the relationship between diabetes and atrial cardiomyopathy in patients with atrial fibrillation, as well as on carbohydrate metabolism disorders in patients with heart failure and acute myocardial infarction. A special place is occupied by papers on various issues of obesity: from the analysis of relationship between the expression of adipocytokines and risk factors for cardiovascular diseases in stable coronary artery disease to the potential of early diagnosis of myocardial fibrosis in patients with epicardial adiposity.

A distinctive aspect of the issue, making it consonant with modern problems of practical health care, is the publication of the design of the international register "Analysis of hospitalizations of comorbid patients infected during the second wave of SARS-CoV-2 outbreak" (AKTIV 2).

The issue shows the experience of foreign authors. In the study by Karalliedde J, an expert opinion on cardio- and nephroprotective effects of glyflozins, in addition to reducing the glycemia level, is presented. Undeniably another landmark work is dedicated to digital health and innovation (Antoniades Ch, et al.). The article is devoted to digital health advances, especially in the field of artificial intelligence, and analysis of medicine areas, where its application is most effective.

Grigory P. Arutyunov

Galina A. Chumakova

As always, we are grateful to all authors for creative approach to work, for relevant, important research, and all readers for their interest in our journal.

Grigory P. Arutyunov, MD, Professor, Corresponding Member of Russian Academy of Sciences
Galina A. Chumakova, MD, Professor

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ORIGINAL ARTICLES
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Novel diagnostic criteria for atrial cardiomyopathy in patients with type 2 diabetes and atrial fibrillation

Polyanskaya E. A., Veklich A. S., Koziolova N. A.

Aim. To determine additional diagnostic criteria for atrial cardiomyopathy in patients with type 2 diabetes (T2D) and paroxysmal/persistent atrial fibrillation (AF).

Material and methods. This cross-sectional screening clinical study included 80 patients with AF and T2D, who were divided into 2 groups depending on the left (LAVI) or right atrial volume index (RAVI) according to echocardiography: the first group included 49 patients with increased LAVI, while the second — 31 patients without changes in LAVI and RAVI. Inclusion criteria were presence of paroxysmal or persistent AF, T2D, age up to 65 years. There were following exclusion criteria: current smoking and less than 1 year old, the presence of cardiovascular and pulmonary diseases, heart failure, implanted artificial pacemaker, prior radiofrequency ablation; valvular heart disease and prosthetics; acute myocarditis, infective endocarditis, hypertrophic, dilated, and restrictive cardiomyopathies, storage diseases, severe liver diseases; thyroid disorders; cancer; acute inflammatory and infectious diseases; alcohol abuse, dementia and mental illness.

Results. The groups did not differ significantly in terms of sex, age, cardiovascular risk factors, risk of stroke and bleeding when using anticoagulants, clinical and laboratory parameters, and the structure of drug therapy. The following parameters significant differ between the groups: LAVI (according to study design), mid-regional pro-atrial natriuretic peptide (MR-proANP), glomerular filtration rate (GFR) calculated by creatinine, tissue inhibitor of matrix metalloproteinases 1 (TIMP-1). For MR-proANP, GFR, TIMP-1, ROC curves were created in order to determine its clinical significance and operational characteristics of parameters. GFR, as a diagnostic criterion, showed unsatisfactory clinical significance when constructing the ROC curve: AUC (area under the curve) was 0,38. The MR-proANP of 62,3-85 pmol/L and TIMP-1 of 156 ng/ml and higher allows verification of atrial cardiomyopathy in patients with T2D and AF at AUC of 0,83 (95% confidence interval (CI), 0,73; 0,92) and 0,90 (95% CI, 0,83; 0,98), respectively.

Conclusion. The blood MR-proANP concentration of 62,3-85 pmol/L is diagnostic for atrial cardiomyopathy in patients with T2D and AF with the sensitivity and specificity of 96,8% and 75,5%, respectively, while TIMP-1 values of 156 ng/ml and above had the sensitivity and specificity of 90,3% and 87,8%, respectively.

Keywords: atrial cardiomyopathy, atrial fibrillation, type 2 diabetes.

Relationships and Activities: none.

E. A. Wagner Perm State Medical University, Perm, Russia.

Polyanskaya E. A. ORCID: 0000-0002-3694-3647, Veklich A. S. ORCID: 0000-0002-8769-7335, Koziolova N. A.* ORCID: 0000-0001-7003-5186.

*Corresponding author: nakoziolova@mail.ru

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In 2016, atrial cardiomyopathy was first presented as any complex of structural, morphological, contractile or electrophysiological changes in the atria that can cause clinically significant manifestations according to the European Consensus of experts [1]. The isolation of this pathology was caused by the fact that there was information on unfavorable prognosis for its development both in relation to chronic heart failure (CHF) and cerebrovascular events, especially at a young age in the presence of genetic diseases [2]. A number of authors suggest that the diagnosis of cardiovascular system pathology at the stage of atrial cardiopathy development will help to see the problem early, which requires the search for therapeutic interventions that can prevent its further progression and adverse outcomes [3, 4].

Experts of the European Consensus distinguish 4 classes of atrial cardiopathy depending on histological changes of the atria and the etiological factor. In patients with isolated form of atrial fibrillation (AF), diabetes mellitus (DM), genetically detected abnormalities, mainly associated with the formation and release of atrial natriuretic peptides (NUP), first-class atrial cardiopathy is isolated [5, 6]. According to the Recommendations of the European Society of Cardiology (2020), the term "isolated AF" is not included in the current classification and is not recommended to use in clinical practice [7]. Experts suggest that at present time, the AF causes in most cases are known and are interrelated with cardiovascular diseases and/or comorbid pathology. At the same time, in the same recommendations, the atrial cardiopathy definition was further developed and discussed. It is noted that atrial cardiopathy at the present stage should be verified on the basis of changes in atrium geometry (dimensions, volume, area).

In addition to atrial imaging techniques, such as speckle tracking during echocardiography (EchoCG), computed tomography and magnetic resonance imaging, inflammation markers (C-reactive protein, cytokines), myocardial stress, adhesion molecules and coagulation factors, as well as collagenolysis system indicators, were studied as potential diagnostic tools of atrial cardiopathy, but mainly separately in individuals with AF or DM [8]. NUPs have been studied primarily in CHF diagnosis, although theoretically their role in atrial cardiopathy detection may be a priority [9]. To verify atrial cardiopathy, many researchers believe that it is necessary to study several biomarkers simultaneously, referring to the multifactorial pathogenesis of its formation [10].

Thus, the identification of new biomarkers of atrial cardiopathy in patients with T2DM and AF, which are likely to take priority of structural changes in the atrium, will allow detecting this pathology at early stage in order to prevent cerebrovascular and cardiovascular complications.

The goal of this study — to detect additional diagnostic criteria for atrial cardiopathy in patients with T2DM and paroxysmal/persistent AF.

Material and methods

A single-stage screening clinical trial was conducted. Within 24 months, the study enrolled 243 consecutive patients admitted to a cardiology hospital due to AF paroxysm. After status stabilization, a cohort of 80 patients with T2DM was identified among them, which were divided into 2 groups depending on indexed volume of left or right atrium (IVLA and IVRA) according to EchoCG data: the first group included 49 patients with an increase in IVLA without an increase in IVRA, the second — 31 patients without changes in IVLA and IVRA. The enrollment criteria were the presence of paroxysmal or persistent AF, T2DM, age up to 65 years. The criteria for non-enrollment were as follows: current and less than 1 year old smoking, presence of cardiovascular and bronchopulmonary diseases, CHF (N-terminal fragment of brain natriuretic peptide (NT-proBNP) >400 pg/ml and/or mid-regional fragment of atrial natriuretic peptide (MR-proANP) >85 pmol/l), implantation of artificial pacemaker, performing radiofrequency ablation in anamnesis; pathology of valves and their prosthetics; acute myocarditis, infectious endocarditis, hypertrophic, dilated cardiomyopathy and restrictive myocardial damages, storage diseases, severe liver diseases; thyroid function abnormalities; oncological diseases; acute inflammatory and infectious diseases; alcohol abuse, dementia and mental diseases that prevent the patient from signing informed consent.

AF was verified by recording a real time 12-channel electrocardiogram. T2DM was detected in accordance with the criteria of the World Health Organization (1999-2013).

EchoCG was performed using a Samsung Accuvix A30 ultrasound scanner (South Korea) in accordance with the recommendations of the American and European Society of Echocardiography. The left ventricular ejection fraction (LV EF) was considered to be preserved by 50% or more, calculated by the Simpsop method. LV diastolic function was assessed by transmitral diastolic blood flow and tissue imaging of diastolic velocities of the mitral annulus. The left ventricular myocardial mass index (LVMMI) was also detected. The criteria for LV hypertrophy were considered to be LVMMI >115 g/m^2 in men and >95 g/m^2 in women, or >50 g/m^{2,7} in men and >47 g/m^{2,7} in women. Atrium enlargement was detected at IVLA >22

Table 1

Clinical and anamnestic characteristics of indicators by examined groups (n=80)

Indicator	Group one (T2DM+AF+IVLA, n=49)	Group two (T2DM+AF, n=31)	P
Age, years	58,2 [46,4; 61,8]	56,9 [43,7; 61,0]	0,238
Women, abs./%	30/61,2	19/61,3	0,819
Men, abs./%	19/38,8	12/38,7	0,819
BMI, kg/m^2	31,2 [27,9; 34,7]	30,2 [27,21; 33,8]	0,341
HR outside of paroxysm in AF, bpm	73,8 [64,5; 79,2]	72,7 [62,6; 80,1]	0,261
SBD, mmHg	131 [116; 145]	130 [111; 142]	0,592
DBP, mmHg	86 [80; 92]	84 [79; 89]	0,620
CHA_2DS_2VASC scale, score	2,1 [1,2; 3,1]	2,0 [1,5; 3,0]	0,874
HASBLED scale, score	1,5 [1,1; 2,7]	1,7 [1,4; 2,6]	0,832
Total cholesterol, mmol/l	5,6 [4,6; 6,2]	5,5 [4,2; 5,9]	0,774
LDL cholesterol, mmol/l	3,4 [2,4; 3,8]	3,2 [2,2; 3,6]	0,673
TG, mmol/l	2,1 [1,6; 2,5]	2,2 [1,5; 2,6]	0,659
HDL cholesterol, mmol/l	1,1 [0,8; 1,4]	1,2 [0,9; 1,4]	0,831
Fasting plasma glucose, mmol/l	8,5 [6,5; 9,4]	8,1 [6,2; 9,7]	0,173
Glycated hemoglobin, %	7,8 [6,8; 8,0]	7,6 [6,7; 8,0]	0,369
HD, abs./%	47/95,9	28/90,3	0,594
CRD, abs./%	9/18,4	6/19,4	0,855
Antiplatelet agents, abs./%	5/10,2	4/12,9	0,993
Anticoagulants, abs./%	36/73,5	21/67,7	0,766
ACE inhibitors/AIIRA, abs./%	44/89,8	25/80,6	0,410
BB, abs./%	35/71,4	15/48,4	0,067
Statins, abs./%	21/42,9	13/41,9	0,881
Calcium antagonists, abs./%	11/22,4	8/25,8	0,941
Antiarrhythmics constantly, abs./%	5/10,2	1/3,2	0,473
Antihyperglycemic drugs, abs./%	44/89,8	30/96,8	0,473
Metformin, abs./%	32/65,3	24/77,4	0,368
Sulfonylurea medications, abs./%	17/34,7	11/35,5	0,867
DPP4i, abs./%	5/10,2	2/6,4	0,863
SLGT2i, abs./%	8/16,3	4/12,9	0,924
Insulin, abs./%	5/10,2	3/9,7	0,760

Abbreviations: AIIRA — angiotensin II receptor blockers, BB — beta-blockers, HD — hypertensive disease, DBP — diastolic blood pressure, CRD — cardiac rhythm disorders, ACE inhibitors — angiotensin-converting enzyme inhibitors, DPP4i — dipeptidyl peptidase 4 inhibitors, BMI — body mass index, SLGT2i — sodium-glucose co-transporter 2 inhibitors, IVLA — indexed volume of left atrium, SAD — systolic blood pressure, DM — diabetes mellitus, TG — triglycerides, AF — atrial fibrillation, HDL cholesterol — high-density lipoprotein cholesterol, LDL cholesterol — low-density lipoprotein cholesterol, HR — heart rate.

ml/m^2 and IVRA >21 ml/m^2 in accordance with the recommendations of the European Society of Echocardiography (2006).

The NT-proBNP and MR-proANP concentration in blood serum was detected after rhythm recovery by ELISA test on the analyzer Immulite 1000 (DPC, USA) using reagents "Biomedica Group" (Austria). The NT-proBNP concentration in serum >400 pg/ml, and MR-proANP >85 pmol/l were considered as diagnostic criteria for CHF in patients with AF [11].

To assess the collagen matrix state, the concentration of a tissue inhibitor of matrix metalloproteinases type 1 (TIMP-1) in blood serum was detected by ELISA test using reagent Aviscera Bioscience (USA) on analyzer Immulite 1000 (DPC, USA). The reference values of TIMP-1 were 111-138 ng/ml.

Statistical processing was conducted using software STATISTICA 12.0 and online calculator Easy ROC_web-tool for ROC curve analysis (ver. 1.3.1). The critical value of the statistical

Table 2

Structural and functional changes of the heart and target organs by groups of subjects (n=80)

Indicator	Group one (T2DM+AF+IVLA, n=49)	Group two (T2DM+AF, n=31)	P
NT-proBNP, pg/ml	96,7 [14,6; 112,7]	88,5 [16,4; 102,9]	0,089
MR-proANP, pmol/l	78,5 [43,7; 80,1]	56,7 [28,7; 61,4]	0,008
LV EF, %	60,8 [53,1; 65,7]	59,2 [52,9; 64,9]	0,384
LVMMI, g/m^2	105,6 [94,2; 128,4]	100,4 [89,7; 126,9]	0,103
LVMMI, g/m^{2,7}	40,9 [34,5; 56,0]	41,0 [37,7; 52,3]	0,286
IVLA, ml/m^2	34,5 [24,6; 48,2]	19,4 [14,0; 20,4]	<0,001
IVRA, ml/m^2	15,9 [12,3; 20,2]	16,8 [13,9; 20,4]	0,098
E/A	1,1 [0,8; 1,2]	1,0 [0,7; 1,2]	0,748
septale e', m/s	8,0 [6,0; 9,0]	7,0 [5,0; 8,0]	0,176
laterale e', m/s	8,0 [7,0; 10,0]	9,0 [8,0; 10,0]	0,105
E/e' average	14,0 [9,0; 16,0]	14,0 [9,0; 15,0]	0,673
Creatinine, μmol/l	91,6 [77,8; 109,2]	87,3 [71,7; 101,4]	0,093
GFRcre, ml/min/1,73 m^2	59,4 [45,7; 84,1]	64,3 [52,0; 89,4]	0,039
TIMP-1, ng/ml	179,0 [148,0; 205,6]	142,2 [126,4; 187,1]	<0,001

Abbreviations: LVMMI — left ventricular myocardial mass index, IVLA — indexed volume of left atrium, IVRA — indexed volume of right atrium, DM — diabetes mellitus, GFRcre — glomerular filtration rate calculated by creatinine, LV EF — left ventricular ejection fraction, AF — atrial fibrillation, A — maximum rate of late LV filling, MR-proANP — mid-regional fragment of atrial natriuretic peptide, NT-proBNP-N — terminal fragment of brain natriuretic peptide, E — maximum rate of early LV filling, e' — early diastolic rate of fibrous ring movement, TIMP-1 — tissue inhibitor of matrix metalloproteinases.

significance level when testing null hypotheses was taken equal to 0,05. The normality of distribution was checked using the Kolmogorov-Smirnov and Shapiro-Wilk criteria. All quantitative features did not correspond to the law of normal distribution and were presented in the form of median, lower and upper quartiles (Me [25; 75]). For qualitative signs, the absolute frequency of the sign, the sign frequency as a percentage (%) were calculated. For distribution of indicators other than normal, statistical processing was carried out using the Mann-Whitney test — for quantitative indicators; the χ^2 test with the Yates correction or the Fisher test for n⩽5 — for qualitative indicators.

The study of relationship between quantitative features was carried out on the basis of Spearman's rank correlation coefficients. Interpretation of the obtained values of statistical relationship test was carried out according to the recommendations of the Rea & Parker. The confidence critical level of null hypotheses in the relationship study was taken as the level of p<0,05.

Detection of the cut-off point corresponding to the optimal value of additional criteria for atrial cardiopathy diagnosis in patients with T2DM and AF was carried out using the method of constructing the ROC curve (receiver operating characteristic), taking into account the Yuden index and detecting the operational characteristics, calculating the quantitative index AUC (Area Under Curve) >0,5 at p<0,05.

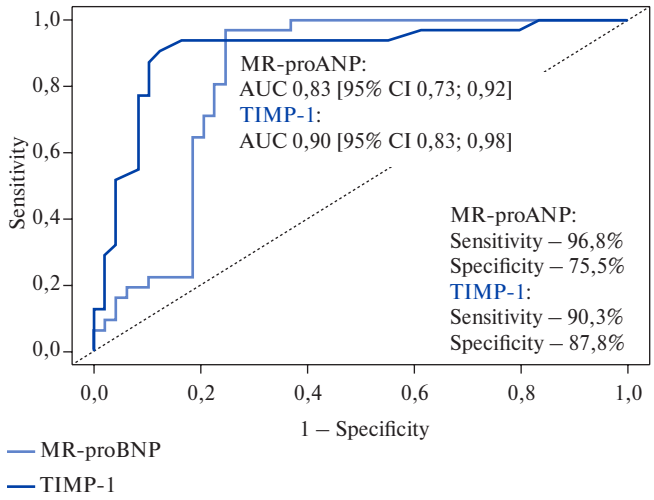

Figure 1. ROC curves for MR-proANP and TIMP-1 in comparison with IVLA as diagnostic criteria for atrial cardiopathy in patients with T2DM and AF (n=80).
Abbreviations: CI — confidence interval, AUC — area under curve, MR-proANP — mid-region fragment of atrial natriuretic peptide, TIMP-1 — tissue inhibitor of matrix metalloproteinases type 1.

The study was controlled by the standards of Good Clinical Practice and the principles of the Helsinki Declaration. The study protocol was promptly appro-

ved by the Ethics Committee. All participants received written informed consent before enrollment.

Results

The clinical and anamnestic characteristics of the enrolled groups of patients are presented in Table 1. The groups did not differ significantly in terms of gender, age, cardiovascular risk factors, risk of stroke and bleeding when using anticoagulants, clinical and laboratory parameters, drug therapy structure.

Structural and functional changes of the heart and target organs by groups of subjects are presented in Table 2.

All patients in the study were found to have preserved LV EF. 51% of patients in the first group and 45,2% of patients in the second group had LV diastolic dysfunction (p=0,779). LV hypertrophy was detected in 40,8% of patients in the first group and in 25,8% of patients in the second group (p=0,259).

Statistically significant differences between the groups were found in the following indicators: IVLA (according to the study design), MR-proANP, glomerular filtration rate (GFR) calculated from creatinine, TIMP-1.

During the correlation analysis, the following data were obtained: direct and inverse relationships of medium and high degree of dependence were revealed, statistically significant relationships between IVLA and MR-proANP (r=0,56; p=0,002), TIMP-1 (r=0,43; p=0,018), GFR (r=-0,37; p=0,012).

ROC curves were constructed for MR-proANP, GFR, TIMP-1 in order to detect the clinical significance and operational characteristics of these biomarkers for atrial cardiopathy diagnosis in patients with T2DM and AF. GFR as a diagnostic criterion demonstrated unsatisfactory clinical significance when ROC curve construction: AUC was 0,38.

When ROC curve construction for all available MR-proANP values up to 85 pmol/l (diagnostic criterion of CHF), a cut-off point of 62,3 pmol/l was obtained. AUC was 0,83 (95% confidence interval (CI) 0,73; 0,92), the standard mean square error of AUC was 0,05 (p<0,001). Therefore, MR-proANP value in the range from 62,3 to 85 pmol/l for the verification of atrial cardiopathy in patients with T2DM and AF allows for diagnostic method sensitivity — 96,8% (95% CI 83,3; 99,9), specificity — 75,5% (95% CI 61,1; 86,7). The ROC analysis for TIMP-1 demonstrated an optimal cut-off point of 156 ng/ml. AUC was 0,90 (95% CI 0,83; 0,98), the standard mean square error of AUC was 0,04 (p<0,001). Therefore, the TIMP-1 value of 156 ng/ml and higher for atrial cardiopathy verification in patients with T2DM and AF allows for diagnostic method sensitivity — 90,3% (95% CI 74,2; 98,0), specificity — 87,8% (95% CI 75,2; 95,4) (Figure 1).

Discussion

In our study, NT-proBNP as an indicator of myocardial stress in heart ventricles was lower than the values corresponding to CHF according to the study design; indicators reflecting LV diastolic dysfunction, LVMMI, did not differ statistically significantly between the groups. Therefore, the value of these indicators as atrial cardiopathy markers in patients with T2DM and AF without CHF is questionable. A number of Russian authors have also demonstrated that NT-proBNP, in contrast to growth differentiation factor-15, is not associated with left atrium fibrosis and its alteration [12]. According to Buttner P, et al. (2018), in 241 patients with AF who underwent catheter ablation, the N-terminal fragment of atrial natriuretic peptide, but not NT-proBNP, was associated with paroxysmal and persistent forms of AF both with an increase in LA diameter and with its normal size (mean values of 15, 20, 19, and 27 ng/ml, respectively, P=0,004) [13]. This is due to the different localization of NUP formation: when the atrial myocardium is stretched, type A NUP is produced, and when the ventricles are stretched, type B NUP is produced.

However, opposite data also exists. Thus, Stanciu AE, et al. (2018) showed that the NT-proBNP concentration increases with increase in left atrium diameter in both paroxysmal and persistent AF [14]. These contradictions are connected to the fact that earlier atrial cardiopathy manifestations without changes in dimetions and volume of the atrium can be electrophysiological atrial disorders detected by voltage mapping in the form of low voltage zones, which reflect the presence of fields of perivascular fibrosis without stretching the myocardial fibers and, accordingly, without increasing the NUP concentration in blood [15]. But even in the range of normal values, as in our study, atrial NPS are statistically significant predictors of atrial fibrosis, detected by voltage mapping [16].

In our study, we obtained a significant prevalence of TIMP-1 in the group of patients with atrial cardiopathy in patients with T2DM and AF. It is well known that both T2DM and AF make a negative contribution to myocardial fibrosis [17]. But in patients with structural remodeling of the left atrium, we obtained higher numbers of TIMP-1, which is an integral indicator of collagen formation in tissues. Similar data were obtained in the study Fragão-Marques M, et al. (2020), which found that patients with AF and aortic stenosis significantly increased

TIMP-1 (p=0,004) in comparison with patients with sinus rhythm [18]. In a large observational study (n=674), it was confirmed that TIMP-1, as well as matrix metalloproteinases, are independent factors of increasing IVLA [19].

The study's limitations are a small sample of patients (n=80), assessment of the predictor value of additional atrial cardiopathy criteria in patients with DM and AF individually, multivariate analysis of biomarkers and instrumental method indicators, such as atrium speckle tracking during EchoCG, voltage mapping during diagnosis of atrial remodeling.

A promising work area should be considered the study of atrial cardiopathy formation not only of the first class, but also in CHF, valvular pathology, amyloidosis and other diseases.

Conclusion

MR-proANP and TIMP-1 as diagnostic methods for detecting atrial cardiopathy in patients with T2DM and AF when constructing the ROC curve showed high clinical significance. MR-proANP concentration in blood in the range from 62,3 to 85 pmol/l for atrial cardiopathy diagnosis in patients with T2DM and AF allows for method sensitivity — 96,8%, specificity — 75,5%, TIMP — 1 156 ng/ml and higher — 90,3% and 87,8%, respectively.

Relationships and Activities: none.

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Glycemia in patients with type 2 diabetes during inpatient treatment for acute myocardial infarction: impact on prognosis

Korotina M. A., Pochinka I. G., Frolov A. A., Botova S. N., Strongin L. G.

Aim. To investigate the relationship between abnormal glycemia levels during inpatient treatment for acute myocardial infarction (AMI) in patients with type 2 diabetes (T2D) and long-term prognosis.

Material and methods. The single-center cohort study included patients with AMI and concomitant T2D who were hospitalized consecutively for 200 days. A total of 237 patients were included. The median number of blood glucose measurements during hospitalization was 15 [8; 20] times. Long-term outcome was estimated at 365 days after hospitalization.

Results. The first glycemic value on admission was 13,6±5,9, while the average glycemia during hospitalization was 10,0±3,5 mmol/L. Within 12 follow-up period, 53 deaths were recorded. It was found that exceeding the glycemic threshold of 10,0 mmol/L in more than 45% of measurements during hospitalization was associated with a 3-fold increase in the risk of an unfavorable outcome within 12 months. Predictors of poor glycemic control are insulin therapy before MI and blood glucose at admission >12,1 mmol/L.

Conclusion. Poor glycemic control (>45% of glucose measurements above the threshold of 10,0 mmol/L) during hospitalization for AMI in patients with T2D is associated with an increased risk of in-hospital death and during the next 12 months, including in patients who underwent endovascular treatment.

Keywords: myocardial infarction, diabetes, glycemic control.

Relationships and Activities: none.

Privolzhsky Research Medical University, Nizhny Novgorod, Russia.

Korotina M. A. ORCID: 0000-0003-1432-2548, Pochinka I. G.* ORCID: 0000-0001-5709-0703, Frolov A. A. ORCID: 0000-0001-7228-7563, Botova S. N. ORCID: 0000-0001-7085-2207, Strongin L. G. ORCID: 0000-0003-2645-2729.

*Corresponding author: pochinka@yandex.ru

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Type 2 diabetes mellitus (T2DM) is a serious medical and social problem, which is due to its high prevalence, a steady trend towards an increase in number of patients and its impact on mortality. The presence of T2DM is associated with an increased risk of acute cardiovascular diseases, in particular, the risk of acute myocardial infarction (AMI) is 1,5-3,0 times higher than in the general population [1]. According to various registers, at least a quarter of all AMI patients suffer from T2DM [2]. At the same time, the mortality rate due to AMI in patients with T2DM, despite the use of modern reperfusion technologies, remains 1,5-2,0 higher than in people without diabetes [3].

There are numerous follows-up demonstrating an association between elevated glycemic levels and an unfavorable prognosis in myocardial infarction (MI) [4]. Experimental studies [5] reveal a direct negative effect of acute hyperglycemia on various processes that can potentially lead to a worse prognosis in AMI, but the true hyperglycemia clinical significance remains unclear. One of the counter-versions is

Table 1

Clinical characteristics of the study cohort

Value		Meaning
Number of patients, n		237
Age, years		68±11
Men/women, n (%)		96 (41%)/141 (59%)
STEMI/NSTEMI, n (%)		134 (57%)/103 (43%)
Duration of hospitalization from the beginning of symptoms, n (%)	<2 hrs	27 (11%)
	2-12 hrs	112 (47%)
	12-24 hrs	39 (16%)
	>24 hrs	59 (25%)
SCG performance, n (%)		173 (73%)
PCI performance, n (%)		136 (57%)
Acute infarction responsible artery, n (%)	ADA	79 (46%)
	Cx	30 (17%)
	RCA	57 (33%)
	MINOCA	7 (5%)
EF, %		47 [40; 54]
Acute heart failure	ALVF	45 (19%)
	Cardiogenic shock	22 (9%)
Atrial fibrillation, n (%)		37 (16%)
Previous myocardial infarction in anamnesis, n (%)		68 (29%)
T2DM duration >10 years, n (%)		67 (28%)
Previous hypoglycemic therapy, n (%)	Insulin	53 (22%)
	Metformin	90 (38%)
	Sulfonylurea	86 (36%)
	DPP4i	6 (3%)
	SLGT2i	3 (1%)
Hypoglycemic therapy in hospital, n (%)	CIIT	4 (2%)
	Basal-bolus insulin therapy	149 (68%)
	Metformin	74 (31%)
	Sulfonylurea	64 (27%)
Maximum troponin I level, pg/ml		11470 [2060; 31420]
eGFR, ml/min		61 [45, 80]

Abbreviations: DPP4i — type 4 dipeptidyl peptidase inhibitors, MINOCA — myocardial infarction without obstruction of coronary artery, NSTEMI — non-ST segment elevation myocardial infarction, STEMI — ST-segment elevation myocardial infarction, SLGT2i — sodium-glucose co-transporter 2 inhibitors, CIIT — continuous intravenous insulin therapy, Cx — circumflex artery, ALVF — acute left ventricular insufficiency, RCA — right coronary artery, ADA — anterior descending artery, eGFR — estimated glomerular filtration rate, T2DM — type 2 diabetes mellitus, SCG — selective coronary angiography, EF — ejection fraction, PCI — percutaneous coronary intervention.

Table 2

Parameters of glycemic control during inpatient treatment for AMI

Value		Meaning
Number of glycemic measurements per 1 patient during inpatient treatment		15 [8; 20]
First value of glycemia at admission, mmol/l		13,6±5,9
Glycemia before leaving the hospital, mmol/l		7,9±3,0
Average glycemia during hospitalization, mmol/l		10,0±3,5
Glycemic variability during hospitalization (SD), mmol/l		2,7±1,7
Number of patients with at least 1 measurement of glycemia <3,9 mmol/l, n (%)		36 (15%)
Percentage of glycemic measurements in the cohort in different ranges	<6,1 mmol/l	13%
	6,1-10,0 mmol/l	49%
	>10,0 mmol/l	38%

Note: SD — standard deviation.

that hyperglycemia in AMI may be not so much a damaging factor as a marker of the severity of AMI and its complications [6]. There are conflicting data on the possibility of improving the prognosis in AMI by actively correcting hyperglycemia [7]. It should be noted that in the works on AMI in patients with diabetes mellitus, glycemia is most often studied during the first days; the relationship between the glycemia level during entire hospital stage and prognosis for MI, as a rule, remains beyond the researchers' interest.

To this date, a consensus on target range of glycemia and how to achieve it in acute coronary syndrome exists. According to the Russian recommendations, the target level of plasma glucose before meals during the day is 6,1-7,8 mmol/l, in the presence of medical and organizational factors that prevent the achievement of strict control of glycemia, its periodic increase to 10,0 mmol/l is acceptable, it is necessary to avoid a decrease in plasma glucose <6,0 mmol/l [8]. Formulated differently, the range of acceptable values is 6,1-10,0 mmol/l. The work presented below examines the issue of how the deviations of glycemia from the target range determine the prognosis of patients with MI.

Goal: to investigate the relationship between the deviations of glycemia from the target range during inpatient treatment for AMI in patients with T2DM and long-term prognosis.

Material and methods

The single-center cohort study included patients with AMI and coexisting T2DM who were sequentially hospitalized in the Regional Vascular Center at the City Clinical Hospital No. 13 of Avtozavodsky district of Nizhny Novgorod for 200 days from January 01, 2018 to July 19, 2018. The study protocol was approved by the Local Ethics Committee of the above-mentioned medical institution. Of the 927 patients with AMI admitted during this period, 237 cases were diagnosed with T2DM (26%), and these patients made up the study cohort. The clinical characteristics of the patients are presented in Table 1. The duration of hospitalization was 11 [9; 14] days. The median number of glycemia measurements during hospitalization was 15 [8; 20] times, at admission, glycemia was examined regardless of the last meal, from the second day, glycemia was examined under fasted conditions and before the main meals. The long-term outcome was assessed at 365 days from the moment of hospitalization.

Quantitative data are presented in the form of medians and interquartile intervals (Median [Q1; Q3]), arithmetic mean ± standard deviation (Mean±SD). Statistical processing was carried out in the program Statistica 10.0 and STATA/MP 16.1. To assess the reliability of differences in quantitative data, the Mann-Whitney test was used, shares — Pearson χ^2, to study the factors that determine the binary outcome — discriminant analysis, to find the optimal cut-off point — ROC analysis, to study survival — the construction of Kaplan-Meier curves, Gehan's-Wilcoxon test and the Cox proportional hazards model.

Results

The main parameters of glycemic control in the study cohort during inpatient treatment for AMI are presented in Table 2.

During hospitalization, 34 patients out of 237 patients with a combination of MI and T2DM died (mortality rate is 14,3%). For comparison: out of 690 patients with MI and without diabetes, death in hospital occurred in 38 cases (mortality

Table 3

Assessment of nformativeness and significance of various factors in relation to unfavorable outcome (discriminant analysis, Wilks' λ: 0,669, F (12,190) =7,875, p<0,001)

Factor	F-remove	p	Tolerance	Multiple correlation coefficient (R^2)
Age	0,021812	0,882	0,819438	0,180562
Anamnesis of MI	1,286801	0,258	0,833960	0,166040
Presence of AF	1,974040	0,162	0,846977	0,153023
Anamnesis of ACA	1,583287	0,209	0,905133	0,094867
STEMI or NSTEMI	0,212681	0,645	0,632060	0,367940
PCI performance	7,087564	0,008	0,778469	0,221531
max troponin	0,013522	0,907	0,716539	0,283461
LV EF	8,770147	0,003	0,835703	0,164297
ALVF and/or cardiogenic shock	7,769934	0,006	0,875151	0,124849
Percentage of glycemic measurements <6,5 mmol/l	0,921981	0,338	0,664080	0,335920
Percentage of glycemic measurements >10,0 mmol/l	7,912016	0,005	0,683180	0,316820
eGFR	4,093605	0,044	0,846277	0,153723

Abbreviations: MI — acute myocardial infarction, STEMI — ST-segment elevation myocardial infarction, NSTEMI — non-ST segment elevation myocardial infarction, ALVF — acute left ventricular insufficiency, ACA — acute cerebrovascular accident, eGFR — estimated glomerular filtration rate, LV EF — left ventricular ejection fraction, AF — atrial fibrillation, PCI — percutaneous coronary intervention, max — maximum value.

was 5,5%, p<0,001, χ^2 Pearson). On the 365th day from the moment of hospitalization, out of 203 discharged patients with T2DM, death occurred in 19 cases (9,4%), thus, the total number of fatal cases during 1 year, taking into account deaths during hospitalization, was 53 (22,3%).

As expected, the level of glycemia at admission, as well as the average glycemia during hospitalization, in patients with an unfavorable outcome were significantly higher compared to the surviving patients — 16,3 [10,8; 21,6] vs 11,6 [9,1; 16,3] mmol/l and 11,7 [9,4; 15,3] vs 8,9 [7,6; 10,5] mmol/l, respectively (for both comparisons, p<0,001, Mann-Whitney). Note the fact that the study cohort was in the acceptable range of glycemia (6,1-10,0 mmol/l) for less than half of hospital stay (49% of all glycemic measurements, Table 2). It goes without saying, the duration of glycemia within the acceptable range for each patient was individual. Therefore, in the future, in accordance with the study goals, the prognosis of patients will be correlated with the proportion of glycemic measurements outside the acceptable range. To assess the contribution of various factors associated with an unfavorable outcome during the follow-up period, a discriminant analysis was used, the results of which are given in Table 3.

Percutaneous coronary intervention (PCI), the presence of acute heart failure (AHF) during AMI, and the left ventricular ejection fraction (EF) had an expected and quite obvious effect on the outcome. The association between the duration of glycemia in the range below 6,1 mmol/l and the adverse outcome was insignificant and unreliable. At the same time, the retention time of glycemia in the range above acceptable values (>10,0) was a strong predictor of death within 1 year (see column F-remove). It can be seen that the factors included in the model are independent (see the columns "Tolerance" and "Multiple correlation coefficient").

To assess the quality of glycemic retention time index >10,0 mmol/l as a predictor of unfavorable outcome, a ROC analysis was conducted. The area

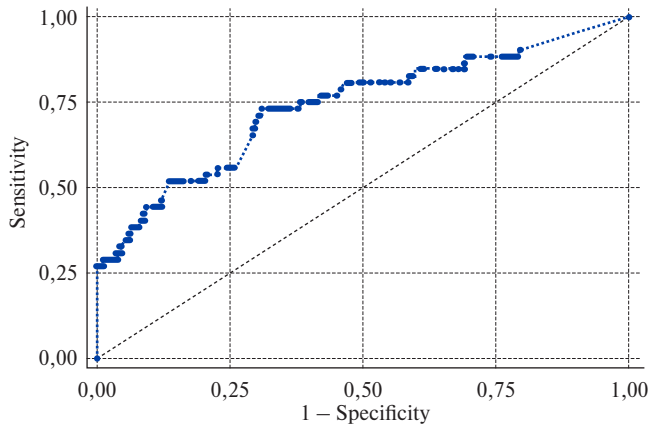

Figure 1. ROC-curve for glycemic retention time >10,0 mmol/l during inpatient treatment for AMI with respect to predicting an adverse outcome over 12 months.

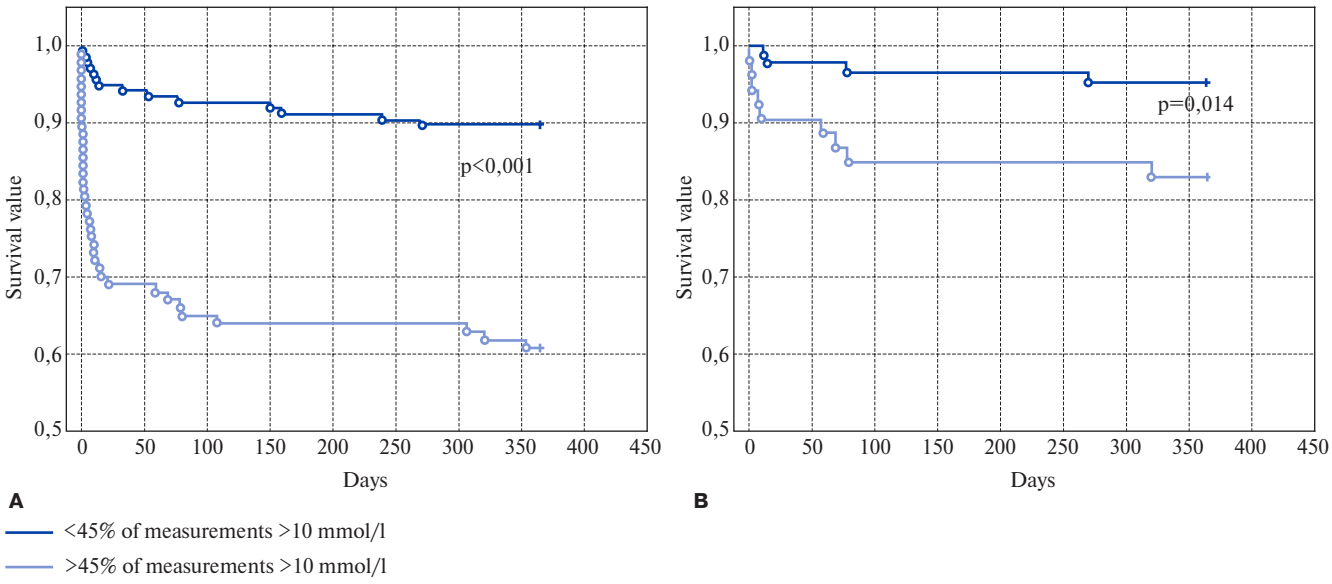

Figure 2. Survival curves (Kaplan-Meier) of patients with different glycemic status **A**) in the general cohort, **B**) in the subgroup with performed PCI (to compare the survival of the Gehans` Wilcoxon test.

Table 4

Results of multivariate regression analysis of 12-month survival (Cox proportional hazard model, p<0,001)

Value	RR	95% RR CI	p
PCI performance (yes/no)	0,32	0,17-0,63	0,001
ALVF and/or cardiogenic shock (yes/no)	4,40	2,38-8,11	<0,001
LV EF <40% (yes/no)	1,58	0,87-2,83	0,129
Percentage of glycemic measurements above 10,0 mmol/l >45% (yes/no)	3,26	1,75-6,09	<0,001
eGFR <55 ml/min (yes/no)	1,93	1,03-3,61	0,041

Abbreviations: CI — confidence interval, ALVF — acute left ventricular failure, eGFR — estimated glomerular filtration rate, LV EF — left ventricular ejection fraction, PCI — percutaneous coronary intervention, RR — relative risk.

Table 5

Results of discriminant analysis of glycemic retention predictors >10,0 mmol/l >45% of the time during hospitalization (Wilks' λ: 0,738, F (7,92) =4,669, p<0,001)

Factor	F-remove	p	Tolerance	Multiple correlation coefficient (R^2)
First value of glycemia at admission	13,61304	<0,001	0,890903	0,109097
max troponin	0,17673	0,675	0,923125	0,076875
Body weight	2,11712	0,149	0,948427	0,051573
ALVF and/or cardiogenic shock	0,02699	0,870	0,902161	0,097839
Pre-admission insulin therapy	6,84471	0,010	0,837085	0,162915
Metformin before admission	3,67191	0,058	0,935785	0,064215
Sulfonylurea before admission	3,79453	0,054	0,820996	0,179004

Abbreviations: ALVF — acute left ventricular failure, max — maximum value.

under ROC-curve was 0,74 (95% confidence interval 0,62-0,82) (Figure 1).

The optimal cut-off point for glycemic residence time above the range of acceptable values in relation to an unfavorable outcome was also determined, it turned out to be 0,45 (sensitivity 73% and specificity 69%), in other words, if a patient with T2DM has >45% of blood glucose measurements during

inpatient treatment for myocardial infarction >10,0 mmol/l, the chances of an unfavorable outcome increase. Indeed, out of 97 patients with >45% of measurements >10,0 mmol/l, death occurred within a year in 38 cases (39%), for comparison — out of 140 patients with <45% of measurements >10 mmol/l, death occurred in 15 cases (11%), p<0,001 (χ^2 Pearson). Importantly, a significant association between sustained hyperglycemia during hospitalization and 1-year prognosis was found not only in the general cohort of patients, but even in the subgroup of patients subjected to PCI, although the number of deaths in this subgroup was naturally lower (Figure 2).

ROC analysis was used to determine the optimal cut-off points for EF and the estimated glomerular filtration rate (eGFR) for an unfavorable outcome during the year. For EF, it was 40% (sensitivity 63%, specificity 79%), for eGFR — 55 ml/min (sensitivity 68%, specificity 73%). A multivariate regression analysis of survival was conducted. The model includes factors determined by discriminant analysis. The results are presented in Table 4. It can be seen that the presence of >45% of glycemic measurements >10,0 mmol/l is accompanied by a more than 3-fold increase in the risk of death within 12 months.

The search for predictors of the presence of glycemia >10,0 mmol/l >45% of the time during hospitalization for AMI was carried out. It is important to include in the model the factors that become available in the next few hours after admission. According to the discriminant analysis results, it was found that such predictors can be considered: 1) the initial (before AMI development) regular use of insulins and 2) the first value of glycemia at admission (Table 5). Note that persistent hyperglycemia during hospitalization does not depend on AMI severity — the level of troponins (indirectly reflects the mass of nonreversibly damaged myocardium) and the presence of AHF in acute stage. Using ROC analysis, the optimal cut-off point for the first glycemic value was determined, it was 12,1 mmol/l (sensitivity 77%, specificity 65%).

Discussion

The study confirmed the presence of a stable association between the glycemia level during hospitalization for AMI in patients with T2DM and the prognosis during the year. It should be emphasized that the importance is not only the first value of glycemia at admission, but also glycemia throughout the inpatient treatment stage. The first value of glycemia at admission always includes a stress hyperglycemia component, is largely determined by severity of hemodynamic disorders and is in some sense a marker of AMI severity (in particular, in patients with acute left ventricular failure and/or cardiogenic shock, the first value of glycemia at admission was 16,3 [10,6; 21,6] vs 11,6 [9,0; 15,8] mmol/l in patients with AMI without AHF, p<0,001 Mann-Whitney). It is obvious that the first value of glycemia at admission is an unmodifiable factor.

In contrast to the first glycemia value at admission, persistent hyperglycemia during the entire inpatient stage of treatment is less dependent on AMI severity. Pay attention to the discriminant analysis results (Table 5) — the presence of glycemia above the range of acceptable recommended values was not determined by either the maximum level of troponin or the presence of AHF. An association of the glycemic measurement proportion above the recommended range not only with mortality rate during hospitalization, but also with a long-term prognosis over the next 12 months indicates in favor of the pathogenetic hyperglycemia value. In other words, the discovered fact allows to consider hyperglycemia in AMI not so much as a marker of stress caused by severe cardiovascular pathology, but as an important and potentially controlled parameter that affects the further disease course. It is equally important that the glycemia state determines the prognosis not only in patients who did not receive endovascular treatment (which provided the greatest contribution to the total number of fatal cases during hospital treatment), but also in patients undergoing PCI (Figure 2 B).

The study answers the question of what predictors of target range critical excess can be detected at the time of admission of a patient with AMI to inpatient hospital. The answer to this question creates prerequisites for determining the phenotypes of patients who need a different approach to the management of glycemia during inpatient AMI treatment. Nowadays recommendations imply variability in hypoglycemic therapy in MI. It seems clear that patients with a dysfunctional phenotype, determined on the basis of identified predictors, will require a more intensive approach to the management of glycemia. Taking into account the discriminant analysis results (Table 5), predictors of unfavorable glycemic profile during inpatient treatment are insulin therapy at the pre-hospital stage and the first value of glycemia at admission >12,1 mmol/l. Such patients constitute an unfavorable phenotype and require more intensive methods of glycemic management from the moment of hospitalization due to AMI.

Study limitations. The result limitations are primarily related to the retrospective nature of the study. The number of glycemic studies varied from patient

to patient. In cases of death on the first day of stay, the number of glycemia studies was obviously insignificant, which could affect the final result. It should also be noted that the study was a single-center study, so the state of glycemic control in AMI described in the article primarily characterizes the routine clinical work of a particular institution and may differ from institutions that use a different practice.

Conclusion

1. Hyperglycemia during inpatient treatment for AMI in patients with T2DM, in contrast to the first value of glycemia at admission, it does not depend on the AMI complications and is not a marker of cardiovascular pathology severity.

2. Bad glycemic control (>45% of glucose measurements above the threshold of 10,0 mmol/l) during AMI hospitalization in patients with T2DM is associated with an increased risk of death in the hospital and during the next 12 months, including in patients who received endovascular treatment.

3. Predictors of bad glycemic control were identified (insulin therapy before AMI, glucose level at admission >12,1 mmol/l), which creates prerequisites for determining the phenotype of patients who need more intensive methods of glycemic management from the moment of admission to the hospital.

Relationships and Activities: none.

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Carbohydrate metabolism disorders in patients with heart failure: data from the local registry

Vaisberg A. R., Tarlovskaya E. I., Fomin I. V., Polyakov D. S., Omarova Yu. V.

Aim. To study the prevalence of carbohydrate metabolism disorders in patients with heart failure (HF) hospitalized in the city HF center.

Material and methods. According to the local registry, the study sequentially included 183 patients (99 men and 84 women) hospitalized in the Nizhny Novgorod city HF center from September 1, 2019. The examination and treatment were carried out in accordance with the current clinical guidelines. In the first 48 hours after hospitalization, the concentration of the N-terminal pro-brain natriuretic peptide, soluble stimulating growth factor 2 (sST2), neutrophil gelatinase-associated lipocalin, cystatin C, blood creatinine was determined. The glomerular filtration rate was calculated using the CKD-EPI equation. To assess the carbohydrate metabolism disorders, all patients were studied for fasting plasma glucose, glycated hemoglobin (HbA_{1c}) and fructosamine.

Statistical data processing was carried out using the R statistics package (R Core Team (2019)).

Results. The incidence of carbohydrate metabolism disorders among patients with decompensated HF was 75,89%, including previously diagnosed type 2 diabetes in 31,25%, newly diagnosed dysglycemia in 44,64% of patients. Less than one fourth of patients had normal parameters of carbohydrate metabolism according to HbA_{1c}, fructosamine and fasting plasma glucose.

The severity of carbohydrate metabolism disorders was significantly correlated with the severity of HF according to the following criteria: 6-minute walk test, HF functional class, sST2 level, and some parameters of cardiac remodeling. Among the criteria used for carbohydrate metabolism disorders, the HbA_{1c} level was most closely associated with the criteria for HF severity.

Conclusion. Carbohydrate metabolism disorders in HF patients are widespread and underdiagnosed during routine examination. The interrelation of carbohydrate metabolism parameters and indicators of HF severity is rationale for active detection of dysglycemia in these patients in order to potentially influence the prognosis.

Keywords: heart failure, carbohydrate metabolism disorders, diabetes.

Relationships and Activities: none.

Privolzhsky Research Medical University, Nizhny Novgorod, Russia.

Vaisberg A. R.* ORCID: 0000-0003-3658-5330, Tarlovskaya E. I. ORCID: 0000-0002-9659-7010, Fomin I. V. ORCID: 0000-0003-0258-5279, Polyakov D. S. ORCID: 0000-0001-8421-0168, Omarova Yu. V. ORCID: 0000-0002-0942-6070.

*Corresponding author: a2912v@mail.ru

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The relevance of studying the problem of carbohydrate metabolism disorders in patients with chronic heart failure (CHF) derived from high prevalence of type 2 diabetes mellitus (T2DM) and prediabetes in patients with CHF, common pathogenesis mechanisms and mutual negative impact on the quality of life and prognosis of patients. The number of patients with T2DM and CHF increases annually both in the Russian Federation and worldwide [1].

Goal: to study the prevalence of carbohydrate metabolism disorders in patients with CHF hospitalized in the city HF center (the State Budgetary Institution of Healthcare of Nizhny Novgorod Region of the City Clinical Hospital No. 38 of the city of Nizhny Novgorod), as well as the relationship between indicators of glycemic status and CHF severity.

Material and methods

The study was carried out in accordance with the Good Clinical Practice standards and the principles of the Helsinki Declaration. The study protocol was approved by the Ethics Committee of FSBEI HE PRMU of the Ministry of Health of the Russian Federation. All participants received written informed consent before enrollment.

The local registry included 183 consecutive patients with CHF of any etiology aged 18 years and older (99 men and 84 women). All patients were treated for CHF decompensation in the Nizhny Novgorod city HF center. The patients were examined and treated in accordance with the existing clinical practice guidelines [2].

Patients underwent echocardiography (EchoCG) on the Vivid3 device (Austria, 2007) by transthoracic method according to the standard protocol with a single-crystal phased sensor SP3-8. In the first 48 hours after hospitalization, the concentration of the N-terminal fragment of the brain natriuretic peptide precursor (NT-proBNP), soluble stimulating growth factor expressed by gene 2 "soluble suppression of tumorigenicity-2" (sST2), neutrophil gelatinase-associated lipocalin (NGal), cystatin C, and blood creatinine was determined, and the glomerular filtration rate was calculated using the formula CKD-EPI. All patients were examined for fasting plasma glucose, glycated hemoglobin (HbA_{1c}), and fructosamine levels. Dysglycemia in this study was understood as T2DM and prediabetes [3]. Carbohydrate metabolism disorder (T2DM and prediabetes) was verified in accordance with the clinical recommendations "Algorithms of specialized medical care for patients with diabetes mellitus" [4]. The NT-proBNP concentration in blood serum was determined by an enzyme immunoassay using a Vector-Best reagent (Russia) on enzyme immunoassay Start Fax-2100. The carbohydrate metabolism disorder incidence was analyzed in patients who met the criteria for CHF at the NT-proBNP level (>125 pg/ml) and the 6-minute walk test (6MWT) (<551 m). The analyzed group included 58 (51,8%) men and 54 (48,2%) women aged 75,0 [65,0; 80,0] years.

Statistical data processing was carried out using the statistical package R [5]. To assess the normal distribution of a quantitative trait, the Shapiro-Wilk test was used, as well as visual assessment of the distribution shape. Descriptive statistics for quantitative features are presented as a median (1st quartile; 3rd quartile), and for nominative features — as a percentage. In assessing the statistical significance level of differences in subgroups, the Mann-Whitney U test was used, and the χ^2 test or the exact Fisher test for small subgroup sizes was used to analyze the frequency differences. In the case of multiple comparisons, the Beniamini-Hochberg multiple comparison correction was applied. Linear regression methods are used in the construction of regression models. The critical level of null hypotheses significance was assumed to be $p<0,05$.

Results

The prevalence of dysglycemia in the examined cohort using the criteria HbA_{1c}, fructosamine and fasting plasma glucose was 75,89%, including 31,25% of patients with previously diagnosed T2DM and 50 patients (44,64%) with first-time dysglycemia. Only 24,11% of patients had normal indicators of carbohydrate metabolism. Among patients with newly diagnosed dysglycemia, only one indicator was deviated from the norm in 26 of 112 patients (23,21%). In 24 (21,43%), 2 indicators were deviated from the norm.

For further analysis, the patients were divided into the following 2 groups: without carbohydrate metabolism disorders and with dysglycemia, including patients with a previously established diagnosis of T2DM. The patients were divided into groups with and without dysglycemia depending on the level of glycolized hemoglobin (Table 1), fructosamine (Table 2), fasting plasma glucose (Table 3).

When divided by HbA_{1c} (Table 1), the obtained data analysis revealed that patients with dysglycemia are younger than patients without carbohydrate metabolism disorders. Patients with carbohydrate metabolism disorders compared with patients with normoglycemia were statistically significantly more likely to belong to the III-IV functional class (FC) of CHF, less often had II FC of CHF, and had lower 6MWT distance indicators. The main

Table 1

Comparative characteristics of clinical, laboratory and instrumental parameters of patients with CHF depending on glycemic status by the level of HbA_{1c}

Indicator	Group 1, n=37	Group 2, n=39	p*
Age, years	77,0 [71,0; 82,0]	71,0 [64,0; 78,0]	0,012
Floor, m/w, abs./%	23/14 [62,2/37,8]	20/19 [51,3/48,7]	0,468
6MWT, m	265 [245; 350]	247 [90,0; 285]	0,016
NYHA I/II/III/IV FC, abs./%	1/11/23/2 [2,7/29,7/62,2/5,41]	0/3/25/11 [0/7,69/64,1/28,2]	0,004
NYHA I/II/III/IV FC, abs./%	12/25 [32,4/67,6]	3/36 [7,69/92,3]	0,016
EF, %	57,0 [46,0; 62,5]	53,5 [38,2; 57,0]	0,060
HFpEF/HFrEF/HFmrEF, abs./%	22/5/4 [71,0/16,1/12,9]	20/11/7 [52,6/28,9/18,4]	0,317
RSCS, points	2,00 [2,00; 3,00]	3,00 [2,00; 3,00]	0,258
LV DD, 0/1/2, abs./%	28/8/1 [75,5/21,6/2,7]	22/15/2 [56,4/38,5/5,13]	0,207
LVMMI, g/m^2	115 [102; 138]	131 [114; 152]	0,197
LALD, mm	45,0 [42,0; 48,0]	48,0 [44,0; 50,0]	0,175
RALD, mm	42,5 [37,5; 46,8]	42,0 [37,0; 44,8]	0,491
IVST, mm	13,0 [12,0; 14,0]	13,5 [11,0; 15,0]	0,804
LVPWT, mm	13,0 [12,0; 13,0]	12,0 [11,0; 14,0]	0,372
LV EDV, ml	96,0 [74,8; 127]	103 [68,5; 152]	0,569
LV ESV, ml	40,5 [27,2; 57,0]	47,5 [30,8; 81,8]	0,355
LV EDD, mm	50,0 [42,0; 53,0]	57,0 [48,0; 61,0]	0,034
LV ESD, mm	33,5 [29,2; 40,8]	44,5 [31,0; 51,0]	0,099
RV, mm	34,0 [31,0; 37,0]	34,0 [30,8; 36,2]	0,659
HbA_{1c}, %	5,30 [5,10; 5,60]	6,00 [5,82; 6,30]	<0,001
Glucose, mmol/l	5,60 [5,10; 6,00]	6,30 [5,20; 7,55]	0,031
Insulin, mME/l	1,96 [1,05; 3,53]	2,92 [1,02; 8,25]	0,143
HOMA index	0,42 [0,23; 0,92]	0,72 [0,25; 2,27]	0,409
Fructosamine, mmol/l	282 [237; 315]	305 [269; 362]	0,028
Cystatin C, mcg/ml	3,00 [2,60; 4,40]	2,80 [2,26; 3,70]	0,259
NGal, ng/ml	26,2 [21,3; 32,2]	25,9 [19,5; 34,9]	0,693
hsCRP, mg/l (lU/l in an.)	11,5 [11,5; 11,6]	11,5 [11,5; 12,4]	0,146
NT-proBNP, pg/ml	1225 [501; 2721]	1967 [959; 2809]	0,149
sST2, ng/ml	25,7 [18,4; 47,5]	41,0 [26,2; 60,9]	0,038

Note: * — significance of differences between groups 1 and 2.

Abbreviations: hsCRP — high-sensitivity C-reactive protein, DD — diastolic dysfunction, LVMMI — left ventricular myocardial mass index, EDV — end-diastolic volume, EDD — end-diastolic dimension, ESV — end-systolic volume, ESD — end-systolic dimension, LV — left ventricle, LALD — left atrium lateral dimension, RV — right ventricle, RALD — right atrium lateral dimension, HFrEF — heart failure with a low ejection fraction, SNpFV — heart failure with an intermediate ejection fraction, HFrEF — heart failure with reduced left ventricular ejection fraction, 6MWT — 6-minute walk test, LVPWT — left ventricular posterior wall thickness, IVST — interventricular septum thickness, FC — functional class, EF — ejection fraction, RSCS — rating scale of clinical state, HbA_{1c} — glycosylated hemoglobin, HOMA-IR — insulin resistance index (Homeostasis Model Assessment of Insulin Resistance; HOMA-IR), NGal — lipocalin associated with neutrophil gelatinase, NT-proBNP — N-terminal fragment of brain natriuretic peptide precursor, NYHA — New York Heart Association, sST2 — soluble circulating form Growth STimulation expressed gene 2.

body of patients in both groups were patients with preserved ejection fraction, but there was a tendency to higher values of ejection fraction in patients with normoglycemia. When analyzing the EchoCG parameters in patients with dysglycemia, there was a statistically significant increase in end-diastolic dimension of the left ventricle (EDDlv). Despite the absence of inter-group differences in NT-proBNP, patients with dysglycemia had a statistically significantly increased sST2.

When dividing patients by glycemic status based on the fructosamine level (Table 2), as in the division by HbA_{1c}, patients with dysglycemia had lower 6MWT values, more often referred to III-IV CHF

Table 2

Comparative characteristics of clinical, laboratory and instrumental parameters of patients with CHF depending on glycemic status when divided by fructosamine level (n=112)

Indicator	Group 3, n=34	Group 4, n=78	p*
Age, years	76,5 [67,2; 82,0]	73,5 [64,0; 79,8]	0,136
Floor, m/w, abs./%	15/19 [44,1/55,9]	43/35 [55,1/44,9]	0,386
6MWT, m	275 [250; 400]	250 [180; 299]	0,008
NYHA I/II/III/IV FC, abs./%	4/8/19/3 [11,8/23,5/55,9/8,82]	1/14/47/16 [1,28/17,9/60,3/20,5]	0,050
NYHA I/II/III/IV FC, abs./%	12/22 [35,3/64,7]	15/63 [19,2/80,8]	0,112
EF, %	54,0 [46,0; 61,0]	55,0 [40,0; 60,0]	0,779
HFpEF/HFrEF/HFmrEF, abs./%	19/5/7 [61,3/16,1/22,6]	43/16/14 [58,9/21,9/19,2]	0,776
RSCS, points	2,50 [2,00; 3,00]	2,50 [2,00; 3,00]	0,669
LV DD, 0/1/2, abs./%	25/8/1 [73,5/23,5/2,94]	52/23/3 [66,7/29,5/3,85]	0,852
LVMMI, g/m^2	121 [108; 142]	124 [105; 150]	0,754
LALD, mm	46,0 [42,8; 50,0]	47,0 [43,0; 50,0]	0,489
RALD, mm	41,0 [36,8; 44,2]	42,0 [38,0; 47,0]	0,428
Pulmonary hypertension 0/1, abs./%	18/16 [52,9/47,1]	24/54 [30,8/69,2]	0,044
IVST, mm	13,0 [12,0; 15,0]	13,0 [11,2; 15,0]	0,845
LVPWT, mm	13,0 [11,0; 14,0]	12,0 [11,0; 13,8]	0,543
LV EDV, ml	90,0 [78,0; 104]	104 [69,0; 151]	0,291
LV ESV, ml	39,0 [31,0; 51,0]	46,0 [28,0; 82,0]	0,273
LV EDD, mm	50,0 [44,0; 53,5]	54,0 [47,0; 61,0]	0,070
LV ESD, mm	35,5 [28,5; 40,8]	38,0 [30,8; 50,0]	0,229
RV, mm	33,0 [30,0; 37,8]	34,0 [31,2; 38,0]	0,464
HbA_{1c}, %	5,30 [5,05; 5,65]	5,70 [5,40; 6,00]	0,010
Glucose, mmol/l	5,55 [4,90; 5,97]	6,00 [5,10; 7,10]	0,033
Insulin, mME/l	1,47 [0,75; 2,66]	2,32 [1,00; 4,60]	0,060
HOMA index	0,34 [0,20; 0,63]	0,64 [0,24; 1,20]	0,126
Fructosamine, mmol/l	244 [230; 260]	309 [289; 344]	<0,001
Cystatin C, mcg/ml	3,00 [1,90; 4,40]	2,80 [2,23; 3,63]	0,595
NGal, ng/ml	22,5 [18,6; 28,2]	25,6 [17,8; 33,5]	0,317
hsCRP, mg/l	11,5 [10,2; 14,0]	11,5 [11,5; 13,4]	0,648
NT-proBNP, pg/ml	1426 [534; 2646]	1375 [621; 2922]	0,653
sST2, ng/ml	28,0 [21,2; 54,2]	38,8 [22,4; 58,1]	0,197

Note: * — significance of differences between groups 3 and 4.

Abbreviations: hsCRP — high-sensitivity C-reactive protein, DD — diastolic dysfunction, LVMMI — left ventricular myocardial mass index, EDV — end-diastolic volume, EDD — end-diastolic dimension, ESV — end-systolic volume, ESD — end-systolic dimension, LV — left ventricle, LALD — left atrium lateral dimension, RV — right ventricle, RALD — right atrium lateral dimension, HFrEF — heart failure with a low ejection fraction, SNpFV — heart failure with an intermediate ejection fraction, HFrEF — heart failure with reduced left ventricular ejection fraction, 6MWT — 6-minute walk test, LVPWT — left ventricular posterior wall thickness, IVST — interventricular septum thickness, FC — functional class, EF — ejection fraction, RSCS — rating scale of clinical state, HbA_{1c} — glycosylated hemoglobin, HOMA-IR — insulin resistance index (Homeostasis Model Assessment of Insulin Resistance; HOMA-IR), NGal — lipocalin associated with neutrophil gelatinase, NT-proBNP — N-terminal fragment of brain natriuretic peptide precursor, NYHA — New York Heart Association, sST2 — soluble circulating form Growth STimulation expressed gene 2.

FC, and the frequency of IV CHF FC was 2 times higher than in normoglycemia. Signs of pulmonary hypertension were found statistically significantly more often in the dysglycemia group and there was a tendency to increase in EDDlv.

The main clinical and laboratory-instrumental characteristics of patients with CHF, depending on glycemic status when divided by fasting plasma glucose level, are presented in Table 3. Patients with dysglycemia were statistically significantly younger, had a statistically significantly greater left ventricular dilatation according to the results of EDDlv and end-systolic dimension of the left ventricle. In the dysglycemia group, there was a tendency to increase

Table 3

Comparative characteristics of clinical, laboratory and instrumental parameters of patients with CHF depending on glycemic status when divided by fasting plasma glucose level (n=112)

Indicator	Group 5, n=52	Group 6, n=60	p*
Age, years	77,0 [67,8; 82,0]	71,0 [64,0; 78,2]	0,047
Floor, m/w, abs./%	27/25 [51,9/48,1]	31/29 [51,7/48,3]	1,000
6MWT, m	265 [238; 350]	260 [145; 300]	0,142
NYHA I/II/III/IV FC, abs./%	3/13/32/4 [5,77/25,0/61,5/7,69]	2/9/34/15 [3,33/15,0/56,7/25,0]	0,068
NYHA I/II/III/IV FC, abs./%	16/36 [30,8/69,2]	11/49 [18,3/81,7]	0,189
EF, %	54,5 [45,8; 60,0]	55,0 [39,8; 60,0]	0,615
HFpEF/HFrEF/HFmrEF, abs./%	31/7/10 [64,6/14,6/20,8]	31/14/11 [55,4/25,0/19,6]	0,411
RSCS, points	2,00 [2,00; 3,00]	3,00 [2,00; 3,00]	0,085
LV DD, 0/1/2, abs./%	41/10/1 [78,8/19,2/1,92]	36/21/3 [60,0/35,0/5,0]	0,099
LVMMI, g/m^2	120 [105; 139]	130 [106; 154]	0,272
LALD, mm	47,0 [42,5; 50,0]	47,0 [43,2; 50,0]	0,624
RALD, mm	42,0 [39,0; 48,5]	42,0 [37,0; 46,0]	0,521
IVST, mm	13,0 [11,5; 14,5]	14,0 [12,0; 15,0]	0,176
LVPWT, mm	12,0 [11,0; 13,0]	12,0 [11,0; 14,0]	0,428
LV EDV, ml	100 [71,0; 127]	89,0 [70,0; 152]	0,540
LV ESV, ml	42,0 [31,0; 57,0]	46,0 [26,0; 82,0]	0,498
LV EDD, mm	49,5 [44,0; 54,0]	56,0 [48,2; 61,0]	0,011
LV ESD, mm	35,0 [29,0; 40,0]	42,0 [31,0; 51,0]	0,048
RV, mm	33,0 [31,0; 38,0]	34,0 [31,0; 39,0]	0,687
HbA_{1c}, %	5,20 [5,00; 5,68]	5,90 [5,60; 6,20]	<0,001
Glucose, mmol/l	5,15 [4,88; 5,60]	6,60 [6,10; 7,43]	<0,001
Insulin, mME/l	1,50 [0,78; 2,83]	3,15 [1,00; 7,32]	0,009
HOMA index	0,35 [0,17; 0,63]	0,84 [0,28; 2,22]	0,006
Fructosamine, mmol/l	275 [244; 304]	305 [267; 348]	0,002
Cystatin C, mcg/ml	2,80 [2,05; 3,26]	2,80 [2,24; 3,71]	0,337
NGal, ng/ml	21,9 [17,6; 27,7]	28,3 [19,1; 34,5]	0,034
hsCRP, mg/l (lU/l in an.)	11,5 [9,65; 13,6]	11,5 [11,5; 14,0]	0,031
NT-proBNP, pg/ml	1024 [498; 2516]	1788 [798; 2962]	0,064
sST2, ng/ml	28,6 [21,2; 47,6]	41,0 [22,8; 80,5]	0,023

Note: * — significance of differences between groups 5 and 6.

Abbreviations: hsCRP — high-sensitivity C-reactive protein, DD — diastolic dysfunction, LVMMI — left ventricular myocardial mass index, EDV — end-diastolic volume, EDD — end-diastolic dimension, ESV — end-systolic volume, ESD — end-systolic dimension, LV — left ventricle, LALD — left atrium lateral dimension, RV — right ventricle, RALD — right atrium lateral dimension, HFrEF — heart failure with a low ejection fraction, SNpFV — heart failure with an intermediate ejection fraction, HFrEF — heart failure with reduced left ventricular ejection fraction, 6MWT — 6-minute walk test, LVPWT — left ventricular posterior wall thickness, IVST — interventricular septum thickness, FC — functional class, EF — ejection fraction, RSCS — rating scale of clinical state, HbA_{1c} — glycosylated hemoglobin, HOMA-IR — insulin resistance index (Homeostasis Model Assessment of Insulin Resistance; HOMA-IR), NGal — lipocalin associated with neutrophil gelatinase, NT-proBNP — N-terminal fragment of brain natriuretic peptide precursor, NYHA — New York Heart Association, sST2 — soluble circulating form Growth STimulation expressed gene 2.

the NT-proBNP level and a significant increase in the sST2 level, a highly sensitive C-reactive protein, and the NGal level.

The most significant differences in the criteria for the severity of CHF, such as 6MWT, prevalence of FC III-IV, EchoCG criteria for LV dilatation (EDDlv), sST2 level, occurred when patients were divided into groups with and without carbohydrate metabolism disorders according to the HbA_{1c} level. Therefore, when analyzing the CHF etiological factors and the therapy conducted before hospitalization, we also took as a basis the division by the HbA_{1c} level (Table 4). In patients with carbohydrate metabolism disorders, the ischemic etiology of CHF was statistically significantly more frequent, and there was a tendency to increase the

Table 4

Comparative characteristics of group 1 and 2 patients depending on carbohydrate metabolism disorders

Indicator	Group 1, n=37	Group 2, n=39	p*
Age, years	77,0 [71,0; 82,0]	71,0 [64,0; 78,0]	0,012
Floor, m/w, abs./%	23/14 [62,2/37,8]	20/19 [51,3/48,7]	0,468
Duration of hospitalization, bed days	9,00 [8,00; 14,0]	11,0 [8,00; 14,0]	0,345
HD, abs./%	35/94,6	39/100	0,234
CAD (angor pectoris), abs./%	17/47,2	24/61,5	0,311
Anamnesis of MI, abs./%	11/29,7	18/46,2	0,216
DCM, abs./%	2/5,41	3/7,69	1,000
DM, abs./%	0/0	35/89,7	<0,001
Paroxysmal/permanent AF, abs./%	8/14 [21,6/37,8]	12/14 [30,8/35,9]	0,641
Anamnesis of TIA/ACA, abs./%	5/13,5	6/15,4	1,000
Ischemic etiology of HF, abs./%	21 [56,8%]	32 [82,1%]	0,032
Anemia, abs./%	14 [37,8%]	10 [25,6%]	0,370
COPD, abs./%	8/21,6	10/25,6	0,887
Pneumonia, abs./%	3 [8,11%]	4 [10,3%]	1,000
Anamnesis of oncological diseases, abs./%	6/16,2	12/30,8	0,222
Obesity 0/I/II/III, abs./%	22/9/3/3 [59,5/24,3/8,11/8,11]	20/12/4/3 [51,3/30,8/10,3/7,69]	0,910
Anamnesis of TG, abs./%	4 [10,8%]	8 [20,6%]	0,166
Joint diseases, abs./%	13 [35,1%]	7 [17,9%]	0,150
CKD 0/1/2/3a/3b/4/5, abs./%	2/3/9/9/8/6/0 [5,41/8,11/24,3/24,3/ 21,6/16,2/0]	0/0/18/11/6/3/1 [0/0/46,2/28,2/15,4/7,69/2,56]	0,094
GFR, ml/min/1,73 $m^2_{(CKD-EPI)}$	55,5 [36,3; 65,3]	55,0 [46,1; 69,6]	0,296
GFR <60 ml/min/1,73 $m^2_{(CKD-EPI)}$, abs./%	22 [59,5%]	23 [59,0%]	1,000
Number of concurrent diseases	5,00 [3,00; 6,00]	5,00 [4,00; 7,00]	0,142
SBD, mmHg	140 [118; 150]	130 [120; 160]	0,742
DBP, mmHg	80,0 [70,0; 90,0]	80,0 [80,0; 90,0]	0,406
HR, bpm	80,0 [78,0; 94,0]	89,0 [76,0; 101]	0,754

Note: * — significance of differences between groups 1 and 2.

Abbreviations: HD — hypertensive disease, DBP — diastolic blood pressure, DCM — dilated cardiomyopathy, CAD — coronary artery disease, MI — myocardial infarction, ACA — acute cerebrovascular accident, SBD — systolic blood pressure, DM — diabetes mellitus, GFR — glomerular filtration rate, HF — heart failure, TIA — transient ischemic attack, AF — atrial fibrillation, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease, HR — heart rate, TG — thyroid gland.

frequency of stage 2-3a chronic kidney disease in the dysglycemia group. The relationship between glycemic status and CHF therapy was not revealed.

Discussion

The high prevalence of dysglycemia (75,89% of patients) in the examined cohort of patients with CHF is comparable both with the results of registers in which the T2DM prevalence is on average 27% compared to 31,25% in our study [6], and with the results of clinical trials in which the prevalence of dysglycemia reached 80% [7-10].

In our study, patients with dysglycemia were statistically significantly younger than patients without carbohydrate metabolism disorders. This does not align with the data on number of clinical trials in which patients with dysglycemia were older [7-10]. Nevertheless, the average age of our patients corresponds to data of international and national epidemiological studies, including EPOCHA-CHF [1, 6].

In our study, patients with impaired carbohydrate metabolism were statistically significantly more likely to have an ischemic etiology of CHF. According to the literature, the ischemic etiology of CHF and the presence of dysglycemia are interrelated, although this may not represent a clear cause-effect mechanism, but rather reflect the general pathogenesis components. Thus, in the Swedish Heart Failure Registry, T2DM was more common in patients with CHD than in patients without it (30% vs 19%) [11].

The severity of carbohydrate metabolism disorders in our study was statistically significantly correlated with the severity of CHF, which does not contradict the data of both heart failure registers and clinical trials that demonstrated that dysglycemia compared to normoglycemia is associated with an increased risk of general and cardiovascular mortality, and in a number of studies, the highest risk of death was observed in patients with newly diagnosed T2DM [7, 8, 10].

When analyzing our data, attention was drawn to a statistically significantly higher level of sST2 in patients with dysglycemia compared to patients without lipid metabolism disorders when divided by the HbA_{1c} level. At the same time, patients with and without dysglycemia did not significantly differ in the NT-proBNP level.

ST2 and NT-proBNP reflect the course of two different but overlapping biological processes, so the markers provide independent and complementary information. As markers of hemodynamic instability or cardiomyocyte stretching, NT-proBNP/BNP are more suitable for the identification of CHF, but are less important for prognosis. ST2 is the most powerful and clinically significant prognostic marker of cumulative cardiovascular events and mortality rate, the degree of sST2 increase does not depend on CHF etiology, as well as on age, gender, heart rate, body mass index, hemoglobin level, and the presence of atrial fibrillation [12].

In our study, among the criteria used for carbohydrate metabolism disorders, the HbA_{1c} level was most closely associated with the criteria for CHF severity.

Some recommendations emphasize that the use of fasting plasma glucose determination, a 2-hour glucose tolerance test, or HbA_{1c} level is equally appropriate [13]. A number of studies substantiate the predominant value of HbA_{1c} as more associated with cardiovascular risk [14].

The stronger association found between HbA_{1c} and emerging cardiovascular diseases may be explained by the ability of HbA_{1c} to reflect average glycemia. Fructosamine values reflect shorter-term glycemic levels than HbA_{1c} — 2-3 weeks. Fructosamine may be a tool of choice when it is necessary to assess glycemic control in patients with severe chronic kidney disease (stages 4 and 5) [15], anemia or hemoglobinopathy [16].

Study limitations. The results of this study should be interpreted in the context of several constraints. This follow-up includes only hospitalized patients with CHF. The patients did not undergo a glucose tolerance test, which could be the reason for underestimating the true prevalence of carbohydrate metabolism disorders.

Conclusion

Thus, according to the local registry, dysglycemia was observed in almost 3/4 of patients with CHF. The severity of carbohydrate metabolism disorders was statistically significantly correlated with CHF severity according to such criteria as 6MWT, CHF FC, sST2 level, and some parameters of heart remodeling. Among the criteria used for carbohydrate metabolism disorders, the HbA_{1c} level was most closely associated with the criteria for CHF severity. Patients with any CHF etiology need to clarify the carbohydrate metabolism status.

Relationships and Activities: none.

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Early diagnosis of myocardial fibrosis in patients with epicardial obesity

Gritsenko O.V.[1], Chumakova G.A.[2,3], Trubina E.V.[1]

It has been proven that about half of patients with heart failure (HF) have a preserved the left ventricle (LV) ejection fraction (EF), which complicates early detection of HF. Currently, there is a search for non-invasive methods for diagnosing myocardial fibrosis at the preclinical heart failure to prevent its progression and the appearance of clinical symptoms.

Aim. To study the relationship of LV mechanics with the level of serum myocardial fibrosis markers in patients with epicardial obesity (EO).

Material and methods. The study included 110 men with general obesity. Depending on echocardiographic data, the patients were divided into 2 groups: EO (+) with epicardial fat thickness (EFT) ⩾7 mm (n=70); EO (-) with EFT <7 mm (n=40). All patients were studied for serum profibrotic markers (MMP-3, collagen I, collagen III, TGF-β, VEGFA, PICP) using enzyme-linked immunosorbent assay. Speckle-tracking echocardiography was used to study LV mechanics (LV twisting, LV twisting rate, time to peak twist, LV untwisting rate, time to peak untwist). The exclusion criteria were the presence of coronary artery disease, hypertension, type 2 diabetes.

Results. In the group of patients with EO (+), a significant increase in the level of all studied profibrotic markers was revealed. According to the results of speckle-tracking echocardiography in the EO (+) group, an increase in the LV untwisting rate to -128,31 (-142,0; -118,0) deg/s^{-1} (p=0,002) and an increase in the time to peak untwist to 476,44 (510,0; 411,0) ms compared to the EO (-) group (p=0,03). A weak significant effect of EFT on LV untwisting rate was revealed in the EO (+) group (r=0,24; p=0,04). In addition, a significant relationship was found between the LV untwisting rate and markers of myocardial fibrosis: MMP-3 (r=0,21; p=0,04) and type III collagen (r=0,26; p=0,03).

Conclusion. Thus, the obtained data suggest that patients with EO have signs of preclinical LV diastolic dysfunction, which are characterized by an increase in LV untwisting rate and level of serum profibrotic factors.

Keywords: obesity, left ventricular mechanics, myocardial fibrosis markers.

Relationships and Activities: none.

[1]Altai Regional Cardiology Dispensary, Barnaul; [2]Research Institute of Complex Issues of Cardiovascular Diseases, Kemerovo; [3]Altai State Medical University, Barnaul, Russia.

Gritsenko O.V.* ORCID: 0000-0001-5937-4128, Chumakova G.A. ORCID: 0000-0002-2810-6531, Trubina E.V. ORCID: 0000-0002-4655-2068.

*Corresponding author: qritzenko.olesia@mail.ru

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Myocardial fibrosis is recognized as a key pathological process in cardiovascular disease development [1, 2]. This is a fundamental process that is observed in heart remodeling and is considered one of the main morphological mechanisms for development of heart failure (CH) with preserved left ventricular ejection fraction (LV EF) (HFpEF) and its progression [3]. Nowadays, an increased interest in the study of LV diastolic dysfunction (DD) is appeared. However, the study of this important pathophysiological aspect is currently complicated by the difficulty of early DD diagnosis. Since LV DD is almost asymptomatic at earliest stages, patients visit a doctor at later stages, when a severe clinical picture is already developing [4]. Traditionally, LV EF is used as the main prognostic indicator of cardiac dysfunction. However, it is becoming increasingly clear that the HF prognosis is not easy to assess only according to LV EF, especially in patients with HFpEF [5]. HFpEF accounts for almost half of HF cases. Concomitant diseases, including obesity, arterial hypertension (AH), and diabetes are key factors in HFpEF onset and progression. Recent evidence suggests that in HFpEF, the degree of myocardial fibrosis is associated with DD degree. In spite of that, the evaluation of fibrosis is not part of everyday clinical practice. First of all, this is due to the difficulties of non-invasive diagnosis of myocardial fibrosis [1]. Classical two-dimensional echocardiography (EchoCG) does not provide information on presence or degree of fibrosis. Available methods of ultrasound diagnostics of LV DD have several algorithms, but there are "blind areas" — combinations of ultrasound signs when LV DD cannot be detected [7-9]. Currently, there is a search for EchoCG methods to detect DD at early stage, since in clinical practice, DD is detected already with sufficiently pronounced fibrosis. These methods include the study of LV mechanics using speckle-tracking EchoCG. In addition, serum markers of myocardial fibrosis are valuable for predicting clinical risk. Extracellular matrix proteins or their cleavage products often enter the systemic circulation and can therefore be measured in serum or plasma. Commonly used fibrosis biomarkers provide insight into collagen production or secretion of non-structural (glyco) proteins that modulate the collagen production itself or its maturation [6].Thus, the search for diagnostic tools for detecting myocardial fibrosis at the initial stages in order to prevent its progression, thereby slowing down the progression of heart failure, is relevant.

Goal of the study: to study the relationship between LV mechanics and the level of myocardial fibrosis serum markers in patients with epicardial obesity (EO).

Material and methods

In this study, from 2016 to 2018, 143 men were enrolled in the Altai Regional Cardiology Dispensary, with an average age of 54,3±8,2 years, who signed an informed consent before being enrolled. The enrollment criteria for patients were the presence of obesity of I-III degree, the average body mass index (BMI) was 33,7±3,3 kg/m^2. The exclusive criteria were the presence of hypertension, coronary atherosclerosis, type 2 diabetes mellitus, as well as the presence of myocardial DD according to transthoracic EchoCG. DD was detected in 33 patients, who were subsequently excluded from the analysis.

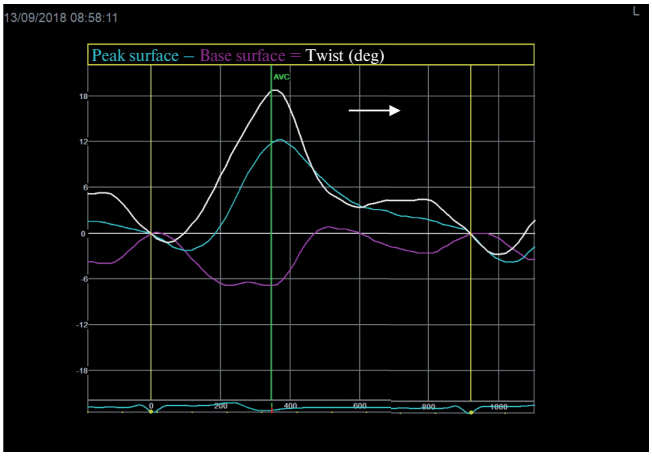


Figure 1. Speckle-tracking EchoCG: LV twist.
Note: the graph shows LV twist in M patient.

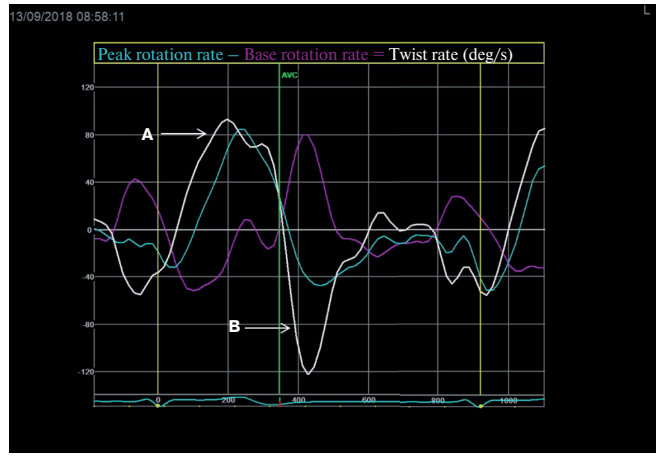


Figure 2. Speckle-tracking EchoCG: LV twisting rate and LV untwisting rate.
Note: the graph below the letter A shows LV twisting rate, under the letter B — LV untwisting rate in M patient.

In all patients, the following laboratory parameters were detected in blood serum using commercially available enzyme immunoassay kits in accordance with the manufacturer's recommendations: levels of type I and III collagen and procollagen I C-terminal propeptide (PICP) were detected using the Cloud-Clone Corp kit (Cloud-Clone Corp., USA); levels of other myocardial fibrosis markers, such as matrix metalloproteinase-3 (MMP-3), transforming growth factor-β (TGF-β), vascular Endothelial growth factor (VEGF-A) was dectected using ebioscience kits (ebioscience, Austria).

The criterion for obesity was BMI ⩾30 kg/m^2 (Society of cardiology of Russian Federation, 2009). BMI was calculated using the formula weight (kg)/ height (m)^2.

All patients underwent EchoCG on the ultrasound system VIVID E95 (GE Healthcare) with matrix sector phased sensor M5Sc (1,5-4,5 MHz). Linear thickness of epicardial adipose tissue (tEAT) as an equivalent of EO was measured in parasternal position along the long LV axis behind free right ventricle wall at the end of systole along the line maximally perpendicular to fibrous ring of aortic valve, which was used as an anatomical landmark in B-mode [10]. The 2016 EACVI recommendations were used to detect LV DD in patients with preserved EF [4]. The rate of LV longitudinal elongation in early diastole (by mitral ring velocity, e'), the ratio of transmitral diastolic flow velocity E to average mitral ring velocity E/e', the left atrium (LA) volume index, and the maximum tricuspid regurgitation rate were

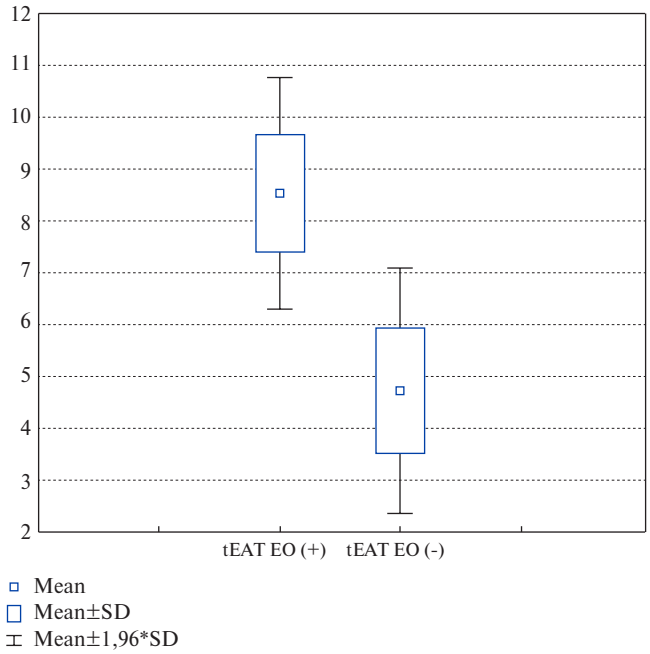


Figure 3. The average values of tEAT in EO (+) and EO (-) groups.
Abbreviations: tEAT — thickness of epicardial adipose tissue, EO — epicardial obesity.

Table 1

Analysis of myocardial fibrosis markers in groups with and without EO

Parameters \ Groups	Group EO (+) (n=70)	Group EO (-) (n=40)	p
MMP-3, ng/ml, (HQ; LQ)	19,47 (24,58; 12,53)	11,16 (13,25; 9,56)	<0,001
Collagen I, pg/ml, M±SD	39958,91±1108,15	25761,30±1885,38	<0,001
Collagen III, pg/ml, M±SD	39821,13±1048,59	28772,25±1090,30	<0,001
TGF-β, ng/ml, M±SD	46,90±1,48	33,62±1,42	<0,001
VEGF-A, pg/ml, M±SD	77,09±1,98	63,74±1,97	<0,001
PICP, pg/ml, M±SD	775,70±17,52	628,07±18,03	<0,001

Note: p — achieved significance level.
Abbreviations: MMP-3 — matrix metalloproteinase-3, EO — epicardial obesity, PICP — procollagen I of C-terminal propeptide, TGF-β — transforming growth factor-β, VEGF-A — vascular endothelial growth factor.

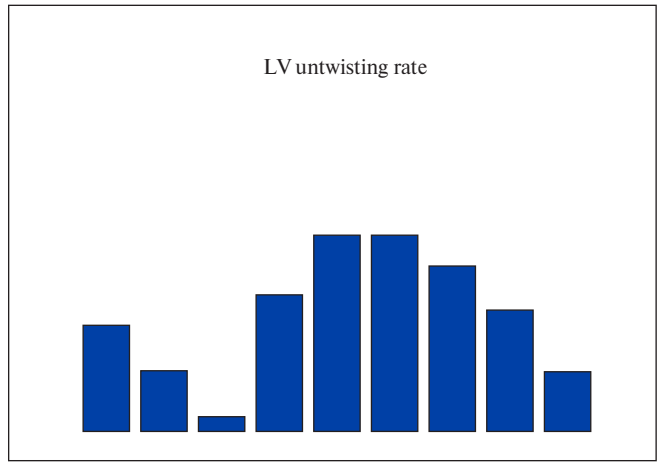
Table 2

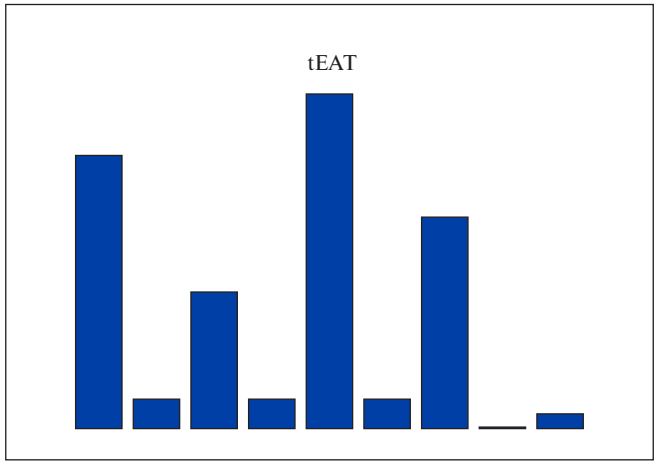
Analysis of EchoCG parameters with and without EO

Parameters \ Groups	Group EO (+) (n=70)	Group EO (-) (n=40)	p
e', cm/s, (HQ; LQ)	0,09 (0,11; 0,09)	0,09 (0,11; 0,09)	0,63
E/e'avg, standard unit, (HQ; LQ)	7,80 (8,90; 6,55)	8,53 (9,70; 7,20)	0,08
Volume index of left atrium, ml/sq^2, (HQ; LQ)	28,39 (31,25; 24,17)	27,82 (30,21; 25,66)	0,55
Maximum speed of tricuspid regurgitation, m/s, (HQ; HQ)	2,78 (2,9; 2,58)	2,67 (2,87; 2,41)	0,13

Note: p — achieved significance level.
Abbreviations: e' — speed of lateral part of mitral valve fibrous ring, E/e'avg — ratio of speed of transmitral diastolic flow to average speed of mitral ring movement, EO — epicardial obesity.

detected [4]. In order to study the LV mechanics, EchoCG was performed in two-dimensional mode according to the standard technique from parasternal access along the short LV axis at the level of mitral valve and apical segments. In the cine loop mode, three cardiac cycles were recorded, and then the LV mechanics were evaluated using ultrasound technology of two-dimensional Speckle Tracking Imaging using an analytical program (EchopacPC, GE Healthcare). The curves obtained at the level of mitral valve and apical segments were used to calculate the LV rotation at the end of systole at the basal (RotMV) and apical (Rotapex) levels, expressed in degrees. Normal apex movement in





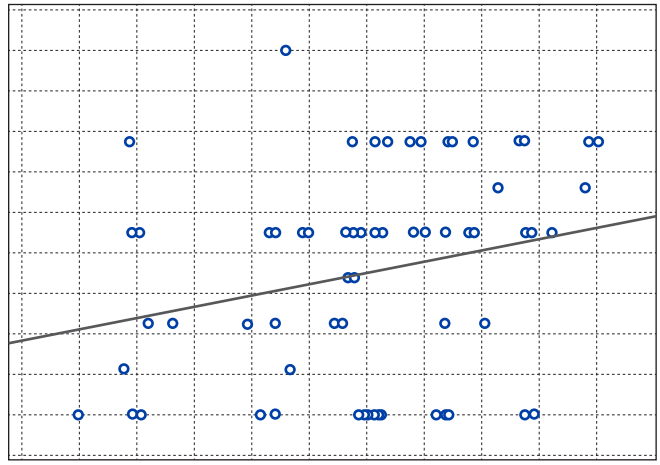


Figure 4. Spearman correlation analysis of LV untwisting rate — tEAT in the group with EO.
Abbreviations: LV — left ventricle, tEAT — thickness of epicardial adipose tissue.

Table 3

Spearman correlation analysis of EchoCG parameters and myocardial fibrosis markers in groups with and without EO

Groups	EO (+) (n=70)				EO (-) (n=40)			
Parameters	e'	E/e'	LA volume index	Maximum TR speed	e'	E/e'	LA volume index	Maximum TR speed
MMP-3, ng/ml	r=-0,10; p=0,39	r=0,09; p=0,48	r=-0,16; p=0,18	r=-0,07; p=0,57	r=0,23; p=0,22	r=-0,10; p=0,58	r=0,05; p=0,79	r=0,10; p=0,59
Collagen I, pg/ml	r=-0,04; p=0,76	r=0,12; p=0,31	r=-0,08; p=0,49	r=-0,06; p=0,64	r=-0,07; p=0,70	r=0,11; p=0,56	r=0,27; p=0,15	r=-0,23; p=0,22
Collagen III, pg/ml	r=-0,01; p=0,94	r=0,08; p=0,49	r=-0,15; p=0,23	r=-0,16; p=0,19	r=-0,14; p=0,44	r=0,15; p=0,41	r=0,25; p=0,17	r=0,32; p=0,08
TGF-β, ng/ml	r=-0,01; p=0,94	r=-0,15; p=0,23	r=-0,23; p=0,05	r=0,12; p=0,31	r=0,25; p=0,17	r=-0,30; p=0,10	r=-0,06; p=0,74	r=-0,15; p=0,41
VEGF-A, pg/ml	r=-0,02; p=0,89	r=-0,09; p=0,42	r=-0,12; p=0,34	r=-0,002; p=0,99	r=-0,15; p=0,42	r=0,16; p=0,40	r=0,31; p=0,09	r=0,34; p=0,06
PICP, pg/ml,	r=0,07; p=0,56	r=0,12; p=0,34	r=-0,03; p=0,79	r=-0,18; p=0,14	r=-0,02; p=0,92	r=-0,04; p=0,82	r=-0,02; p=0,90	r=0,10; p=0,59

Note: p — achieved significance level, r — rank correlation coefficient.
Abbreviations: LA — left atrium, MMP-3 — matrix metalloproteinase-3, TR — tricuspid regurgitation, EO — epicardial obesity, PICP — procollagen I of C-terminal propeptide, TGF-β — transforming growth factor-β, VEGF-A — vascular endothelial growth factor, e' — speed of lateral part of mitral valve fibrous ring, E/e'avg — ratio of speed of transmitral diastolic flow to average speed of mitral ring movement.

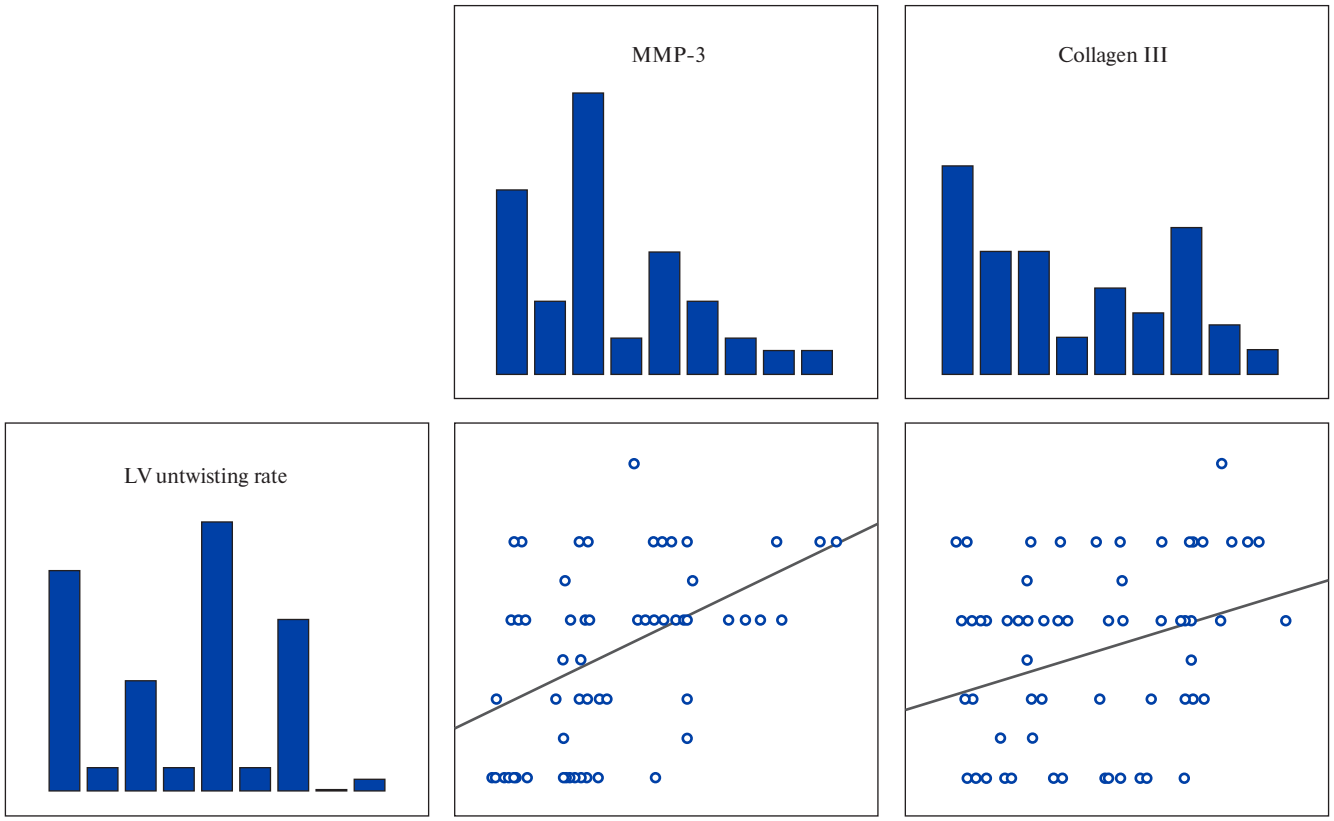


Figure 5. Spearman correlation analysis of LV untwisting rate with markers of myocardial fibrosis in both groups.
Abbreviations: LV — left ventricle, MMP-3 — matrix metalloproteinase-3.

Table 4

Analysis of LV mechanics indicators in both groups

Parameters \ Groups	Group EO (+) (n=70)	Group EO (-) (n=40)	p
Twisting, deg, (HQ; LQ)	19,56 (22,0; 17,36)	15,39 (21,0; 11,8)	0,14
Twisting speed, deg/s^{-1}, (HQ; LQ)	118,70 (124,7; 101,70)	97,25 (117,0; 85,0)	0,16
Time to twist peak, msec, (HQ; LQ)	186,90 (224,0; 148,0)	179,44 (214,0; 131,0)	0,83
Untwisting rate, deg/s^{-1}, (HQ; LQ)	-128,31 (-142,0; -118,0)	-89,68 (-89,0; -78,75)	0,002
Time to untwisting peak, msec, (HQ; LQ)	476,44 (510,0; 411,0)	402,50 (361,0; 415,0)	0,03

Abbreviation: EO — epicardial obesity.

systole implies counterclockwise movement, is plotted on the graph as a curve directed upward from the isoline, and is evaluated as a positive value. Normal basal areas rotation is associated with a clockwise movement, which is shown on the graph as a downward curve and is evaluated in negative values. The resulting LV twist was quantified as the degree-expressed rotation of apex minus the value of rotation at the basal level [11] (Figure 1, 2). The LV twisting rate (deg/s^{-1}), the time to LV twisting peak (as the first positive peak after R wave on electrocardiogram, msec), the untwisting rate (during early diastole, deg/s^{-1}) and the time to LV untwisting peak (as the first negative peak after aortic valve closure, msec) [12].

In order to exclude AH, including masked forms, daily blood pressure monitoring was performed with the device MD-01M (Russia).

To exclude atherosclerotic damage of coronary arteries, patients were given either multispiral computed tomography of coronary arteries or coronary angiography, according to the indications. Multispiral computed tomography of coronary arteries was carried out using a multispiral X-ray computed tomograph from Toshiba (Japan), a 64-slice tomograph with data processing at the workstation VITREA, and the

coronary angiography Integris 3000 by Philips (the Netherlands).

Depending on presence or absence of EO, patients were divided into two groups: EO (+) with tEAT ⩾7 mm (n=70) and EO (-) with a tEAT <7 mm (n=40). EO was considered an increase in tEAT ⩾7 mm, which in clinical trials showed an association with the risk of developing insulin resistance, dyslipidemia, and other metabolic disorders [13]. The selected groups did not differ in age, gender, systolic and diastolic blood pressure, waist circumference and hip circumference, BMI.

Statistical data processing was carried out with the help of the program STATISTICA 10. For each of the continuous quantities with a normal distribution, the mean (M) and standard deviation (SD) are given, for quantities with an abnormal distribution, the median (Me) and the upper and lower quartiles (HQ; LQ) are given. The normal distribution hypothesis was checked using the Shapiro-Wilk test. Statistical description of relationship between the various parameters was carried out by calculating the Spearman rank correlation coefficient. The level of statistical significance was assumed to be $p<0,05$.

Results and discussion

When comparing the average values of tEAT in the selected groups, it was found that in the group EO (+), it was 1,8 times greater than in the group EO (-), and amounted to 8,54 (7,0; 9,0) mm, and in the group EO (-) — 4,74 (4,0; 6,0) mm, $p<0,001$ (Figure 3).

When studying the features of changes in the level of myocardial fibrosis serum markers, a statistically significant increase in the level of all the studied markers was revealed in the group EO (+) compared to the group EO (-) (Table 1).

When analyzing the echocardiography data, it was revealed that the selected groups did not have statistically significant differences in such parameters as e', E/e', LA volume index, and maximum tricuspid regurgitation rate (Table 2).

A correlation analysis was performed between the EchoCG parameters (e', E/e', LA volume index, maximum tricuspid regurgitation rate) and the level of myocardial fibrosis markers. Correlations between the studied parameters in both groups were not revealed (Table 3).

When assessing the average parameters of LV mechanics in the group EO (+), an increase in the LV untwisting rate by 1,4 times and an increase in the time to LV untwisting peak by 1,2 times were revealed (Table 4).

The correlation analysis revealed that in the group EO (+), there is a weak statistically significant effect of tEAT on the LV untwisting rate ($r=0,24$; $p=0,04$), while in the EO (-) group, there is no such effect (Figure 4).

When assessing the relationship between LV mechanics indicators associated with LV diastolic function (LV untwisting rate and time to peak of LV untwisting) and serum markers of myocardial fibrosis, the Spearman correlation analysis was performed and positive statistically significant relationship between LV untwisting rate and matrix metalloproteinase-3 (MMP-3) ($r=0,21$; $p=0,04$), as well as with type III collagen ($r=0,26$; $p=0,03$) in the group EO (+), no relationships were found with other markers of myocardial fibrosis. No such relationships were observed in the group EO (-) (Figure 5).

Violation of LV DD is formed in the early stages of course of many diseases connected to cardiovascular system. The influence of obesity on development and progression of lipotoxic myocardial fibrosis and DD has been proven. Considering the fact that there are currently no non-invasive methods aimed at early detection of myocardial fibrosis, the morphological basis of DD, with the subsequent HF development, we made an attempt to assess the levels of pro-fibrotic markers in patients with and without EO, to assess the parameters of LV mechanics that characterize LV diastolic function, and to identify the relationship between these parameters. In our study, it was shown that in patients with EO, the level of all studied serum markers of myocardial fibrosis (MMP-3, collagen I, collagen III, TGF-β, VEGF-A, PICP) increases. When assessing the parameters of LV mechanics, which change at the earliest stages of myocardial damage, it was found that the LV untwisting rate and the time to LV untwisting peak increased, while the EchoCG indicators recommended for LV DD detection were not changed. Our data is consistent with the literature data. Thus, in a study conducted by Ahmed MK, et al., aimed at studying the mechanics of LV in DD, it was shown that the LV untwisting rate and the time to LV untwisting peak in the early DD stages (with impaired relaxation) increase, then these indicators decrease in the course of HF progression, and these indicators normalize or decrease in patients with an E/A value >1,5 [14].

Conclusion

Thus, the data obtained by us showed that the enrolled patients with EO have signs of preclinical LV DD. The relationship between the LV untwisting rate and MMP-3, type III collagen, was revealed, while there is no relationship between these markers and traditional EchoCG criteria for LV DD. The obtained data suggest that the determination of the

level of myocardial fibrosis serum markers, as well as the determination of the LV untwisting rate and the time to LV untwisting peak using speckle-tracking EchoCG, which reflect the mechanical DD aspect, can be used as additional markers for DD detection at the preclinical stage.

Relationships and Activities: none.

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Biomarkers of inflammation, parameters characterizing obesity and cardiac remodeling in patients with atrial fibrillation and metabolic syndrome

Ionin V. A.[1], Barashkova E. I.[1], Zaslavskaya E. L.[1], Nifontov S. E.[1], Bazhenova E. A.[1,2], Belyaeva O. D.[1,2], Baranova E. I.[1,2]

Aim. To determine the blood level of inflammatory markers, parameters characterizing obesity and cardiac remodeling in patients with atrial fibrillation (AF) in combination with metabolic syndrome (MS).

Materials and methods. This single-stage case-control study included 677 subjects aged 35 to 65 years: patients with MS (n=407), of which 128 patients with AF; comparison group — patients with AF without MS (n=75); control group — practically healthy subjects without cardiovascular diseases and metabolic disorders (n=195).

Results. It was found that the blood concentration of circulating pro-inflammatory biomarkers in patients with AF and MS is higher than in patients with AF without MS: C-reactive protein (CRP) (4,43 (2,68-4,98) and 2,33 (1,08-4,7) mg/L, p<0,0001), interleukin-6 (IL-6) (2,5 (1,28-5,13) and 1,27 (0,68-2,7) pg/ml, p<0,0001) and tumor necrosis factor-α (TNF-α) (5,18 (2,63-7,32) and 3,42 (2,11-5,48) pg/ml, p<0,0001). The serum CRP concentration positively correlates with left (ρ=0,451, p<0,0001) and right atrial (ρ=0,412, p<0,000) volumes, as well as with the waist circumference (ρ=0,503, p<0,001) and epicardial fat thickness (ρ=0,550, p<0,001). Plasma IL-6 and serum TNF-α levels correlated to a lesser extent with parameters characterizing atrial remodeling, but had a strong positive relationship with epicardial fat thickness. According to multivariate analysis, it was found that an increase in the epicardial fat thickness had a greater effect on an increase in blood concentration of CRP, IL-6 and TNF-α, in contrast to other parameters characterizing obesity, such as body mass index and waist circumference.

Conclusion. An increase in the blood concentration of proinflammatory biomarkers CRP, IL-6, and TNF-α is associated with cardiac remodeling and epicardial fat thickness in patients with MS and probably has a pathogenetic role in increasing the AF risk in this cohort of patients.

Keywords: C-reactive protein, interleukin-6, tumor necrosis factor-alpha, atrial fibrillation, metabolic syndrome.

Relationships and Activities: none.

[1]First Pavlov State Medical University, St. Petersburg; [2]Almazov National Medical Research Center, St. Petersburg, Russia.

Ionin V. A.* ORCID: 0000-0001-7293-1144, Barashkova E. I. ORCID: 0000-0002-7888-4374, Zaslavskaya E. L. ORCID: 0000-0002-1209-7765, Nifontov S. E. ORCID: 0000-0002-8857-7992, Bazhenova E. A. ORCID: 0000-0003-1419-6860, Belyaeva O. D. ORCID: 0000-0002-5349-2227, Baranova E. I. ORCID: 0000-0002-8788-0076.

*Corresponding author: ionin.v.a@gmail.com

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Atrial fibrillation (AF) — the typically common adult arrhythmia, the prevalence of which has been increasing in recent decades [1]. Non-modifiable risk factors (RF) for AF include male gender, old age, and hereditary predisposition; potentially modifiable causes predisposing to AF include arterial hypertension (AH), obesity, diabetes mellitus (DM), dyslipidemia, obstructive sleep apnea syndrome, chronic heart failure, valvular heart disease, and others [2]. The mechanisms of AF formation are different: the formation of automatism foci in the area of pulmonary veins entry and the circulation of excitation waves in atria, impaired functioning of L-type calcium channels, the formation of dilatation and fibrosis of the left atrium (LA), etc. Once it occurs, this arrhythmia usually anticipates ("fibrillation is born in fibrillation") [3]. However, despite significant advances in understanding the arrhythmogenesis mechanisms underlying the AF formation, the pathogenesis of this arrhythmia is not completely clear. Of particular interest is the possible role of obesity as one of the most common and potentially modifiable AF RF.

The incidence of obesity, as well as AF, progressively increases and takes epidemic form [1]. It should be noted that obesity, especially visceral (abdominal), is often combined with hypertension and metabolic disorders, combined with the concept of "cardiometabolic syndrome". According to the IDF criteria (2005), metabolic syndrome (CMS) is diagnosed in the presence of three or more of the following five factors: abdominal obesity, AH, hyperglycemia or DM, hypertriglyceridemia, and a decrease in the concentration of high-density lipoprotein cholesterol. According to the Atherosclerosis Risk in Communities (ARIC) study, the presence of CMS increases the risk of AF by 1,7 times [4]. AH and abdominal obesity (the most common components of CMS) favor the cardiac remodeling formation, causing dilatation, LP fibrosis, and AF development. However, to date, it is not entirely clear whether AF is a consequence of CMS or whether individual CMS components favor the development of this arrhythmia.

Inflammation plays a significant role in the development and progression of cardiovascular diseases, including AF [5, 6]. In AF, a significant inflammation role has also been established, as evidenced by the data of a meta-analysis conducted by Wu ZK, et al. [7]. Schnabel RB, et al. previously reported 12 markers of inflammation circulating in the blood associated with AF [8]. In AF, the role of two biomarkers of inflammation — C-reactive protein (CRP) and interleukin-6 (IL-6) — has been most studied [9, 10]. In addition to these parameters, the association between AF and tumour necrosis factor-α (TNF-α), interleukin-8 (IL-8) and interleukin-2 (IL-2) was studied [6, 11]. Leukocytosis and distortion of the ratio between neutrophils and lymphocytes is also an indicator of systemic inflammation and oxidative status, which, in turn, favor the AF development [11]. Obesity and CMS are also characterized by asymptomatic chronic inflammation, with these diseases, an increase in the blood of circulating markers of inflammation, including IL-6, CRP, and TNF-α [12, 13].

In AF, the role of not only systemic, but also local inflammation caused by the influence of epicardial adipose tissue (EAT) is discussed. In visceral obesity and CMS, the volume of epicardial fat is increased [14, 15]. In patients with CMS, the increase in EAT thickness estimated by echocardiography, is AF RF [16]. EAT secretes proinflammatory cytokines (TNF-α, IL-6, IL-1β, etc.) [17], which can cause local inflammation and participate in the formation of atrial fibrosis — a substrate for AF development [13, 18]. A meta-analysis conducted by Antonopoulos AS and Antoniades C testifies that a large volume of EAT is associated with AF development [19].

Therefore, it can be believed that the systemic and local inflammation specifically attributed to CMS can cause atrial cardiomyopathy, which can favor AF development [14]. Previously, only a few studies have compared the levels of pro-inflammatory and anti-inflammatory cytokines in patients with AF in combination with CMS with the concentration of these cytokines in patients with isolated AF or with CMS without arrhythmia, and the data from these studies are ambiguous [20, 21]. Based on the fact that the previously published data are contradictory or were obtained according to small samples of patients, this study was conducted.

The study's goal was to determine the levels of biomarkers of inflammation in the blood, parameters that characterize obesity and heart remodeling, in patients with AF in combination with CMS.

Material and methods

In the period from 2014 to 2018, 1307 patients with AF who were hospitalized in the medical department of the university clinic were examined. 721/1307 (55,2%) patients were diagnosed with CAD, 46/1307 (3,5%) with valvular pathology, and 80/1307 (6,1%) patients had inflammatory heart diseases. The one-time cohort examination enrolled patients with isolated AF (n=75) and patients with AF in combination with CMS (n=128) and without structural heart disease. The experimental groups included patients with CMS without AF (n=279), as well as those examined without CMS and AF and without other significant pathology (n=195).

The study was performed in accordance with the standards of Good Clinical Practice (GCP) and the Helsinki Declaration principles. The study protocol was approved by the Ethics Committees of all participating centers. All participants received written informed consent before enrollment.

The study enrolled men and women aged 35 to 65 years. Patients with CMS had 3 or more components of this syndrome diagnosed according to the IDF criteria (2005). The study excluded patients with verified chronic heart failure, heart valve pathology, systemic and oncological diseases, as well as with chronic kidney disease, liver pathology with impaired liver function, thyroid diseases, disorders of cerebral circulation, operations or interventional interventions on the heart in the anamnesis. Acute and exacerbations of chronic inflammatory diseases were excluded in all the examined patients, and patients with an increase in the CRP level determined by a highly sensitive method, >10 mg/l, were not included. The work assessed anthropometric and laboratory parameters, the results of instrumental study methods: electrocardiography, echocardiography (EchoCG). The EchoCG protocol is performed in standard modes on the Vivid 7 device (GE, USA). The thickness of epicardial fat (TEF) was measured over the right ventricle free wall in parasternal position in the diastole in three heart cycles. EAT was identified as a hypoechoic space anterior to the right ventricle free wall, and its thickness was measured between the epicardial heart surface and the pericardium parietal leaf.

All blood serum and plasma samples were centrifuged and stored at a temperature of -40° C, followed by determination of studied biomarkers concentration using standard ELISA test sets. The TNF-α concentration in blood serum was determined by a highly sensitive enzyme immunoassay (Human TNF alpha High Sensitivity ELISA kit, Bender MedSystems, Austria), with a minimum detection threshold of 0,13 pg/ml. The IL-6 concentration in blood plasma was determined by a highly sensitive ELISA test (Human IL-6 High Sensitivity ELISA kit, Bender MedSystems, Austria), with a minimum detection threshold of 0,03 pg/ml. The CRP level in blood serum was determined by a highly sensitive immunoturbidimetric method using COBAS INTEGRA of Roche Diagnostics GmbH, Germany, the minimum concentration of determination is 0,15 mg/l.

All the study results were entered into the original database. The normality of numerical variables distribution was conducted using the Kolmogorov-Smirnov criteria. Depending on type of distribution, the quantitative variables obeying the normal distribution law are represented by the mean value (M) ± standard deviation (σ). For comparison in independent groups of indicators with a normal distribution, the parametric unpaired Student's t-test was used. For the distribution of quantitative indicators that differ from the normal, the data are presented as a median (Me) with the indication of interquartile intervals (25-75%), and for comparison in independent groups of such indicators, the nonparametric Mann-Whitney U-test was used. Multiple comparisons in groups (more than two) in parametric statistics were conducted using univariate analysis of variance (ANOVA), and for nonparametric statistics — the Kruskal-Wallis test. In assessing the correlation coefficient significance, the Pearson's (r) criteria for the normal distribution and Spearman (ρ) criteria for the abnormal distribution of indicators were used. The statistical analysis was performed using the licensed IBM SPSS Statistics software, version 22.0.

Results

The study groups were comparable in gender distribution and did not differ significantly in age. When comparing the parameters characterizing atrium remodeling, it was found that the volumes and volume indices of both atria in patients with AF in combination with CMS are greater than in patients with this arrhythmia without CMS. Differences in the size and volume of atrium in the groups of patients with CMS without AF and CMS with AF were not identified. When TEF comparing, it was found that this index is higher in patients with AF in combination with CMS than in patients with AF without CMS (5,8±2,7 and 3,4±1,6, p<0,0001). In patients with AF without CMS, the TEF index was higher than in healthy subjects (3,4±1,6 and 2,3±0,9, p<0,0001). The main clinical, laboratory and EchoCG characteristics of the examined patients are presented in Table 1.

The concentrations of inflammatory biomarkers in blood serum and plasma in patients with AF in combination with CMS were higher than in patients with AF without CMS: CRP (4,43 (2,68-4,98) and 2,33 (1,08-4,7) mg/l, p<0,0001), IL-6 (2,5 (1,28-5,13) and 1,27 (0,68-2,7) pg/ml, p<0,0001) and TNF-α (5,18 (2,63-7,32) and 3,42 (2,11-5,48) pg/ml, p<0,0001). The levels of these biomarkers are also higher in patients with AF and CMS than in patients with CMS without AF: CRP (4,43 (2,68-4,98) and 2,46 (1,23-3,92) mg/l, p<0,0001), IL-6 (2,5 (1,28-5,13) and 2,12 (1,17-3,56) pg/ml, p<0,0001) and TNF-α (5,18 (2,63-7,32) and 3,5 (2,39-5,6) pg/ml, p<0,0001). The IL-6 concentration in patients with AF without CMS was lower than in patients with CMS without this arrhythmia (1,27 (0,68-

Table 1

Clinical, laboratory, and echocardiographic characteristics of patients with CMS and AF

Parameters	CMS (-), AF (-), n=195, (1)	CMS (+), AF (-), n=279, (2)	CMS (-), AF (+), n=75, (3)	CMS (+), AF (+), n=128, (4)	Statistical significance, p
Age, years	51,3±8,6	53,7±9,3	55,6±6,8	54,3±7,2	p>0,05
Gender, male/female	80/115	125/154	30/45	74/54	p>0,05
BMI, kg/m^2	22,5±4,8	34,1±8,6	24,9±3,5	32,3±6,6	$p_{1,2}$<0,0001; $p_{1,3}$=0,098; $p_{1,4}$<0,0001; $p_{2,3}$=0,003; $p_{2,4}$=0,089; $p_{3,4}$<0,0001
Waist circumference, cm	79,5±8,1	114,8±11,5	86,7±11,7	111,9±13,5	$p_{1,2}$<0,0001; $p_{1,3}$ =0,071; $p_{1,4}$<0,0001; $p_{2,3}$<0,0001; $p_{2,4}$=0,059; $p_{3,4}$<0,0001
Total TC, mmol/l	4,9±0,9	5,4±1,1	4,8±1,2	5,2±1,2	$p_{1,2}$<0,0001; $p_{1,3}$=0,821; $p_{1,4}$<0,0001; $p_{2,3}$<0,0001; $p_{2,4}$=0,689; $p_{3,4}$<0,0001
LDL TC, mmol/l	2,8±0,3	3,4±0,3	3,1±0,3	3,1±0,4	$p_{1,2}$<0,001; $p_{1,3}$<0,001; $p_{1,4}$<0,001; $p_{2,3}$=0,134; $p_{2,4}$=0,289; $p_{3,4}$=0,989
HDL TC, mmol/l	1,6±0,3	1,2±0,3	1,4±0,3	1,1±0,4	$p_{1,2}$<0,001; $p_{1,3}$=0,145; $p_{1,4}$=0,001; $p_{2,3}$=0,089; $p_{2,4}$=0,689; $p_{3,4}$=0,001
TG, mmol/l	1,0±0,3	2,1±0,8	1,3±0,4	1,7±1,2	$p_{1,2}$<0,001; $p_{1,3}$=0,585; $p_{1,4}$=0,001; $p_{2,3}$=0,001; $p_{2,4}$=0,001; $p_{3,4}$=0,001
Glucose, mmol/l	4,7±0,6	6,1±1,2	5,1±0,4	6,0±1,4	$p_{1,2}$<0,0001; $p_{1,3}$=0,087; $p_{1,4}$<0,0001; $p_{2,3}$=0,001; $p_{2,4}$=0,678; $p_{3,4}$=0,001
Echocardiography					
LA diameter, mm	34,9±2,7	44,6±4,2	43,2±2,0	44,5±4,0	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,678; $p_{2,4}$=0,838; $p_{3,4}$=0,345
LA volume, ml	43,2±9,4	81,9±16,6	60,4±19,8	79,9±19,4	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,001; $p_{2,4}$=0,388; $p_{3,4}$=0,001
LA volume index, ml/m^2	24,3±4,9	39,2±9,7	30,4±9,0	40,1±11,2	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,001; $p_{2,4}$=0,624; $p_{3,4}$=0,001
RA volume, ml	41,3±8,9	68,5±14,4	57,5±20,6	65,9±14,7	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,001; $p_{2,4}$=0,457; $p_{3,4}$=0,001
RA volume index, ml/m^2	23,4±4,3	31,9±7,3	29,2±8,8	32,8±7,8	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,001; $p_{2,4}$=0,314; $p_{3,4}$=0,001
LV MMI, g/m^2	82,6±14,3	105,3±15,3	105,1±17,8	112,9±16,3	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,893; $p_{2,4}$<0,0001; $p_{3,4}$<0,0001
	70,5±12,4	96,3±7,3	82,9±14,7	105,4±12,4	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,001; $p_{2,4}$<0,0001; $p_{3,4}$<0,0001
LV EF, %	64,3±7,1	61,2±6,4	62,4±4,2	60,8±6,2	p>0,05
TEF, mm	2,3±0,9	4,3±2,4	3,4±1,6	5,8±2,7	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,01; $p_{2,4}$<0,0001; $p_{3,4}$<0,0001
Duration of AF, years	-	-	4,9±1,2	4,2±2,2	p>0,05
AF form -	-	40/75 (53,3%)	78/128 (60,9%)	p>0,05	
-	-	20/75 (26,7%)	31/128 (24,3%)	p>0,05	
		15/75 (20%)	19/128 (14,8%)	p>0,05	

Abbreviations: LV MMI — left ventricular myocardial mass index, BMI — body mass index, LDL — low — low-density lipoproteins, HDL — high-density lipoproteins, LA — left atrium, CMS (-) — not available metabolic syndrome, CMS (+) — available metabolic syndrome, RA — right atrium, TG — triglycerides, TEF — thickness of epicardial fat, LV EF — left ventricular ejection fraction, AF (-) — not available atrial fibrillation, AF (+) — available atrial fibrillation, TC — cholesterol.

Table 2

Proinflammatory biomarkers in patients with AF and CMS

Biomarkers	CMS (-), AF (-), n=195, (1)	CMS (+), AF (-), n=279, (2)	CMS (-), AF (+), n=75, (3)	CMS (+), AF (+), n=128, (4)	Statistical significance, p
NLR	1,75 (1,42-2,22)	1,56 (1,26-2,1)	1,71 (1,42-2,14)	1,75 (1,42-2,53)	p>0,05
ESR, mm/h	8,1 (4,5-13,5)	13,5 (7,1-18,0)	11,2 (5,0-15,0)	12,7 (5,0-18,1)	$p_{1,2}$<0,001; $p_{1,3}$<0,001; $p_{1,4}$<0,001; $p_{2,3}$=0,537; $p_{2,4}$=0,787; $p_{3,4}$=0,236
Fibrinogen, g/l	2,9±0,8	3,5±0,8	3,1±0,7	3,3±0,9	p>0,05
CRP, mg/ml	0,57 (0,33-1,19)	2,46 (1,23-3,92)	2,33 (1,08-4,7)	4,43 (2,68-4,98)	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,617; $p_{2,4}$<0,0001; $p_{3,4}$<0,0001
IL-6, pg/ml	0,64 (0,34-1,57)	2,12 (1,17-3,56)	1,27 (0,68-2,7)	2,5 (1,28-5,13)	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,005; $p_{2,4}$=0,022; $p_{3,4}$<0,001
TNF-α, pg/ml	2,22 (0,91-3,38)	3,5 (2,39-5,6)	3,42 (2,11-5,48)	5,18 (2,63-7,32)	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,266; $p_{2,4}$=0,001; $p_{3,4}$=0,001

Abbreviations: IL-6 — interleukin 6, CMS (-) — not available metabolic syndrome, CMS (+) — available metabolic syndrome, NLR — neutrophil-lymphocyte ratio, ESR — erythrocyte sedimentation rate, CRP — highly sensitive C-reactive protein, TNF-α — tumor necrosis factor-α, AF (-) — not available atrial fibrillation, AF (+) — available fibrillation atria.

Table 3

Correlations of biomarkers with parameters of atrial remodeling in the examined patients

Biomarkers	LA size	LA volume and volume index	RA volume and volume index	LV MMI	LV EF
Neutrophil/ Lymphocyte	-0,01, p=0,852	-0,02, p=0,717 0,03, p=0,609	-0,02, p=0,706 -0,06, p=0,912	0,005, p=0,991	-0,005, p=0,919
ESR, mm	0,07, p=0,209	0,06, p=0,291 0,118, p=0,04	-0,04, p=0,936 0,06, p=0,292	0,037, p=0,514	-0,04, p=0,458
Fibrinogen, g/l	0,075, p=0,332	0,154, p=0,04 0,116, p=0,135	0,102, p=0,205 0,044, p=0,582	0,144, p=0,06	-0,005, p=0,948
CRP, mg/ml	0,486, p<0,0001	0,451, p<0,001 0,326, p<0,001	0,427, p<0,001 0,296, p<0,001	0,412, p<0,0001	-0,124, p<0,0001
IL-6, pg/ml	0,393, p<0,0001	0,342, p<0,001 0,256, p<0,001	0,304, p<0,001 0,229, p<0,001	0,361, p<0,0001	-0,059, p=0,296
TNF-α, pg/ml	0,334, p<0,0001	0,254, p<0,001 0,206, p<0,001	0,221, p<0,001 0,159, p<0,001	0,243, p=0,004	-0,117, p=0,238

Abbreviations: IL-6 — interleukin 6, LV IMM — left ventricular myocardial mass index, LP — left atrium, Nf/Lf — neutrophil-lymphocyte ratio, RA — right atrium, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, LV EF — left ventricular ejection fraction, TNF-α — tumor necrosis factor-α.

2,7) and 2,12 (1,17-3,56) pg/ml, p<0,005), and the concentrations of TNF-α in patients with CMS without AF and AF without CMS did not significantly differ, as shown in Figure 1. The rate of erythrocyte sedimentation in patients in the CMS and AF groups was higher than in healthy subjects, but the average values were within the reference range. Differences in neutrophil-lymphocyte ratio and level of fibrinogen in the examined groups were not established. The data is presented in Table 2.

The correlation analysis of the relationship between the studied inflammation biomarkers and the parameters characterizing atrial remodeling (Table 3), revealed a positive relationship to a greater extent between CRP, IL-6 and TNF-α and the LA size and volume than with the volume of right atrium (RA). According to the results of correlation analysis of inflammatory biomarkers with indicators characterizing obesity, a positive relationship between CRP and IL-6 with body mass index (BMI), waist circumference (WC) and TEF was established. The TNF-α concentration was weakly correlated with BMI and WC, in contrast to the stronger relationship with TEF, as presented in Table 4. The IL-6 and CRP concentrations in blood also correlated more strongly with TEF than with BMI and WC (Figure 2).

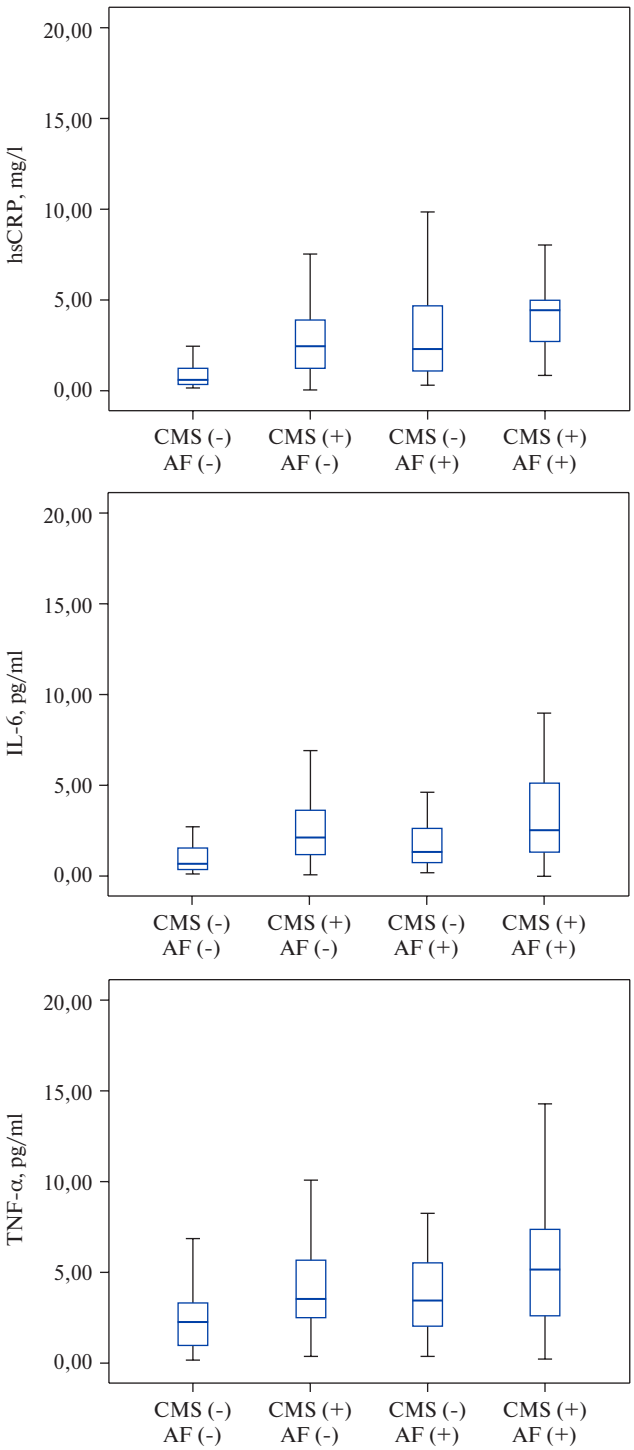

Figure 1. Concentrations of CRP, TNF-α in serum and IL-6 in blood plasma of patients with AF, CMS and practically healthy subjects.
Note: hsCRP — highly sensitive C-reactive protein, IL-6 — interleukin-6, CMS (-) — not available metabolic syndrome, CMS (+) — available metabolic syndrome, AF (-) — no atrial fibrillation, AF (+) — available atrial fibrillation, TNF-α — tumor necrosis factor-α.

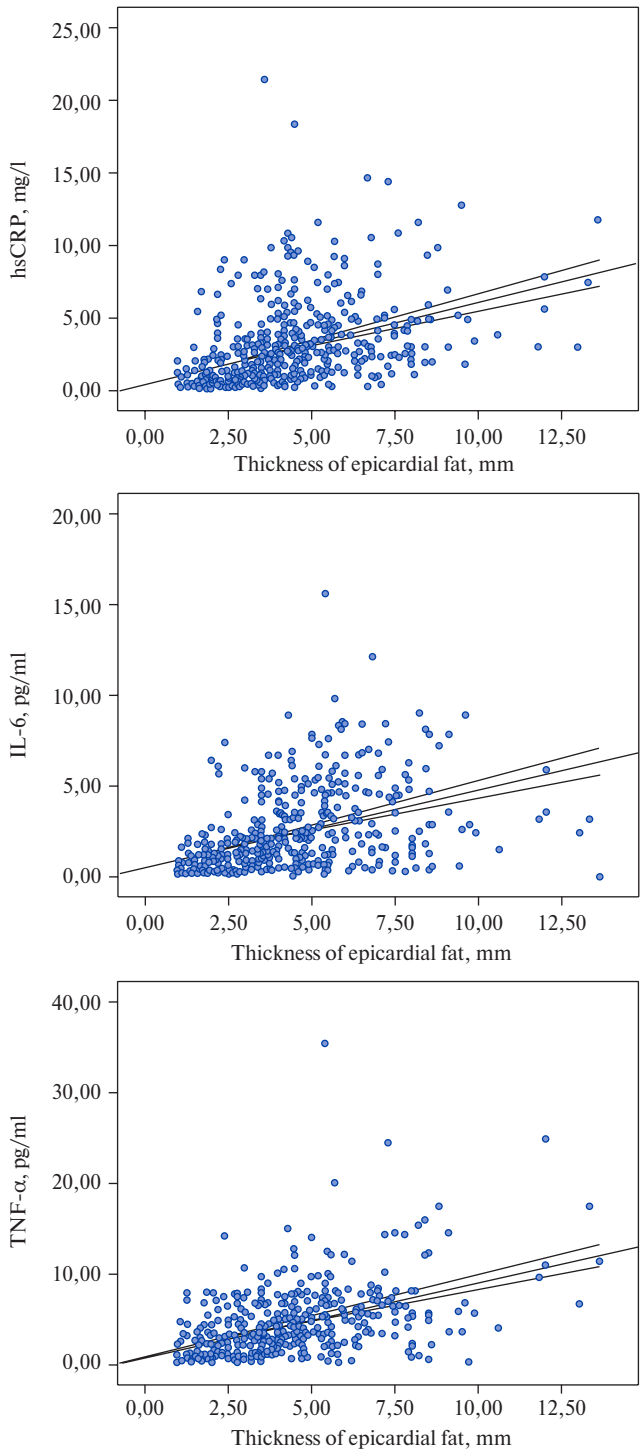

Figure 2. Correlation of inflammatory biomarkers concentrations (CRP, IL-6, TNF-α) with TEF.
Abbreviations: IL-6 — interleukin-6, hsCRP — highly sensitive C-reactive protein, TNF-α — tumor necrosis factor-α.

Multivariate linear regression analysis found that TEF has a statistically more significant effect on the increase in the concentration of CRP, IL-6 and TNF-α than BMI and WC (Table 5). When comparing the concentrations of inflammation studied biomarkers in patients with different TEF, divided by quartiles, it was found that a progressive

Table 4

Correlations of biomarkers with parameters characterizing obesity in the examined patients

Biomarkers	BMI	WC	TEF
Neutrophil/Lymphocyte	-0,122, p=0,02	-0,06, p=0,251	-0,05, p=0,394
ESR, mm	0,129, p=0,02	0,109, p=0,06	0,172, p=0,006
Fibrinogen, g/l	0,241, p=0,0009	0,318, p=0,0002	0,249, p=0,002
CRP, mg/ml	0,504, p<0,0001	0,503, p<0,0001	0,550, p<0,0001
IL-6, pg/ml	0,413, p<0,0001	0,405, p<0,0001	0,525, p<0,0001
TNF-α, pg/ml	0,264, p<0,0001	0,284, p<0,0001	0,508, p=0,0002

Abbreviations: IL-6 — interleukin 6, BMI — body mass index, Nf/Lf — neutrophil-lymphocyte ratio, WC — waist circumference, ESR — erythrocyte sedimentation rate, CRP-C — reactive protein, TEF — thickness of epicardial fat, TNF-α — tumor necrosis factor-α.

Table 5

Linear regression analysis of the influence of parameters characterizing obesity on inflammation biomarkers

Biomarkers	BMI	WC	TEF
CRP, mg/ml	0,208, p=0,003	0,028, p=0,699	0,265, p<0,0001
IL-6, pg/ml	0,001, p=0,985	0,132, p=0,094	0,355, p<0,0001
TNF-α, pg/ml	-0,043, p=0,572	0,06, p=0,446	0,436, p<0,0001

Abbreviations: IL-6 — interleukin 6, BMI — body mass index, WC — waist circumference, CRP — C-reactive protein, TEF — thickness of epicardial fat, TNF-α — tumor necrosis factor-α.

Table 6

Concentrations of inflammatory biomarkers in the blood of the examined patients with different TEF

TEF, quartiles	⩽2,6 mm (Q1)	2,7-3,8 mm (Q2)	3,9-5,0 mm (Q3)	⩾5,0 mm (Q4)	Statistical significance, p
CRP, mg/ml	0,59 (0,32-1,31)	1,23 (0,89-2,99)	2,7 (1,37-4,55)	3,4 (2,03-5,1)	p<0,0001
IL-6, pg/ml	0,61 (0,34-1,34)	1,4 (0,83-2,15)	2,3 (1,22-3,47)	3,34 (1,51-5,34)	p<0,0001
TNF-α, pg/ml	1,83 (0,89-3,19)	2,71 (1,48-4,15)	3,95 (2,81-5,45)	5,65 (3,48-7,89)	p<0,0001

Abbreviations: IL-6 — interleukin-6, CRP — C-reactive protein, TEF — thickness of epicardial fat, TNF-α — tumor necrosis factor-α.

increase in CRP, IL-6 and TNF-α is observed in each TEF quartile, which is presented in Table 6.

Discussion

A large number of studies have been devoted to the role of chronic asymptomatic inflammation in AF development and progression in recent years [3, 6, 11]. Strong evidence of a pathogenetic link between chronic inflammation and AF is that the incidence of AF in diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and others is significantly higher than in the general population [6]. Systemic inflammation also relates to the AF molecular mechanisms development in obesity. Obesity is considered today as a "chronic inflammation" status [22]. Undoubtedly, a relationship between obesity and an increased risk of cardiovascular disease, including AF is largely determined by the high level of inflammatory mediators [23].

The recommendations of the European Society of Cardiology 2020 on the AF diagnosis and treatment contain information on the risk of developing this arrhythmia, including the CMS components: hypertension, obesity, diabetes and dyslipidemia [2]. According to the ARIC study, CMS increases the risk of AF by 1,7 times [4]. The most common CMS components are abdominal (visceral) obesity and AH. Abdominal obesity and CMS are characterized by an imbalance of adipokines, in particular, hyperleptinemia and a decrease in the concentration of protective cytokine — adiponectin. Previously, it was proved that leptin and adiponectin are independently associated with the inflammatory marker

level [13]. CMS is associated with increased levels of proinflammatory cytokines (IL-6, TNF-α), as well as adipokines (leptin, ghrelin), uric acid, and decreased levels of anti-inflammatory cytokines (IL-10) [24].

The literature contains indications of single studies that compared the levels of pro-inflammatory and anti-inflammatory cytokines in patients with AF in combination with CMS and with concentration of these cytokines in patients with isolated AF or with CMS without arrhythmia [20]. In particular, Itani HA, et al. examining the concentration of 13 pro-inflammatory and anti-inflammatory cytokines in a small sample of 71 patients, found that the blood concentration of anti-inflammatory cytokines IL-4 and IL-10 in patients with isolated AF is higher than in patients with CMS or CMS in combination with AF [20]. In the same study, there was a tendency, which did not reach significance, to higher values of proinflammatory cytokines IL-6, TNF-α, and interferon-gamma (IF-γ) in patients with combination of AF and CMS in comparison with isolated AF and isolated CMS [20]. In our work on a large sample (482 patients and 195 examined from the comparison group), it was shown that in patients with AF in combination with CMS, the concentrations in blood plasma of IL-6 and in blood serum of CRP and TNF-α are significantly higher than in patients with isolated arrhythmia or in patients with isolated CMS, and also significantly higher than in patients without arrhythmia, without hypertension and metabolic disorders.

IL-6 — a pro-inflammatory cytokine, synthesized in immune cells, in particular, in macrophages, monocytes and fibroblasts, as well as in non-immune cells — endotheliocyte, vascular smooth muscle cells. IL-6 — the main inflammatory response regulator, which promotes the synthesis in hepatocytes of several proteins of the acute inflammation phase, such as CRP, fibrinogen, etc. [10]. IL-6 stimulates janus kinase/signal transducers and transcription pathway activators (JAK/STAT). Previous studies indicate that IL-6 in plasma is elevated in AF [9, 12, 20]. The high level of IL-6 and other proinflammatory cytokines in the blood in CMS is due to adipocyte dysfunction and is associated with an increase in subpopulation of macrophages in adipose tissue. In turn, proinflammatory cytokines induce insulin resistance. In particular, IL-6 increases insulin resistance, is associated with certain components of CMS, as well as high concentrations of this adipokine are associated with the severity of CMS manifestations [12, 13].

CRP is associated with the level of adipokines, leptin, favors an increase in CRP, and adiponectin suppresses the CRP synthesis and secretion [13]. In our study, the highest values of CRP were diagnosed in patients with AF in combination with CMS. CRP — the most significant indicator of vascular inflammation and is synthesized in the liver in response to stimulating factors, in particular, IL-6, synthesized by macrophages and adipocytes, which explains the low-intensity inflammation characteristic of obesity [13]. Mazidi M, et al. was found that in adults in the USA, the CMS risk was 5,2 times higher in the subjects belonging to the quartile with the highest concentration of CRP in blood plasma, compared with the quartile of subjects with the lowest value of this indicator [25]. In a cohort study conducted in Korea, it was found that a high level of CRP is the AF RF in the population [26]. A large prospective study conducted in China found that patients with CMS combined with elevated levels of CRP (>3 mg/l), in contrast to CMS with CRP ⩽3 mg/l, the AF risk is 1,61 times higher [21]. Previously, it was found that the CRP level is significantly higher in patients with AF with recurrent arrhythmia after radiofrequency ablation of the area of pulmonary veins [6, 8, 11]. However, the pathogenetic relationship between CRP and AF is not fully clear. It is assumed that CRP binds to membranes of cardiomyocytes, activates the compliment, and is a trigger of tissue damage [11].

TNF-α — a cellular signaling protein involved in the inflammatory cascade is secreted by macrophages, lymphocytes, including in adipose tissue, and stimulates the activation of transcription nuclear factor (NF-kB). IL-6 and TNF-α have a proinflammatory effect, stimulate fibroblast differentiation, proliferation, and migration. TNF-α is also a pyrogenic substance and stimulates the CRP synthesis in the liver. In combination with other adipokines, IL-6 and TNF-α also favor the CMS progression, disrupting the regulation of synthesis and release of adipokines and playing a decisive role in the progression of insulin resistance [20]. Similarly to other inflammation markers, TNF-α levels are higher in patients with AF [11].

In this work, positive correlations were found between the concentrations of inflammatory markers in the blood plasma — CRP, IL-6 and the parameters that characterize the heart remodeling — the LA size and volume, the mass index of left ventricle myocardium. These data indirectly confirm the relationship of IL-6 and other inflammation markers with the heart remodeling characteristic of AF, and are consistent with the literature data [20]. High levels of IL-6 are also associated with AF relapse after electrical cardioversion and catheter radiofrequency ablation [7], with thromboembolic complications and outcomes of this arrhythmia [10].

Of particular importance is the fact that our study revealed significant correlations between CRP, IL-6, TNF-α and the parameters characterizing obesity, including those with TEF. At the same time, it was found that in patients with a combination of AF and CMS, the thickness of epicardial fat is significantly greater than in patients with CMS without arrhythmia and in patients with AF without CMS. EAT — a truly visceral adipose tissue directly adjacent to myocardium, including atrial myocardium, which is important in AF formation, especially in patients with visceral obesity [18]. EAT synthesizes a large number of different molecules — pro-and anti-inflammatory adipokines, growth factors, and fibrogenic substances that have paracrine and vasocrine effects on the myocardium [3]. The expression level of most cytokines in EAT is much higher than in visceral fat of a different localization. Macrophages and T-lymphocytes, including those that migrate from EAT to the myocardium, are able to secrete proinflammatory and fibrogenic substances [3]. Consequently, inflammation favors the development of myocardial fibrosis and the formation of electroanatomic substrate for the AF appearance and progression [3]. This position is confirmed by the study of Abe I, et al. (2018), who evaluated the EAT thickness and the severity of LA auricle fibrosis (according to intraoperative biopsy data) in AF, and found that the severity of EAT thickness and fibrosis is associated with the prevalence of LA myocardial fibrosis [27]. In addition, the content of collagen in the LP myocardium positively correlated with the concentration of proinflammatory cytokines in the blood — IL-6, TNF-α [27]. Inflammatory mediators not only stimulate the replacement of cardiomyocytes with fibrous fibers, which is a key mechanism of structural remodeling in AF, but also affect the ion currents in the channels and ATP-regulated pumps, which together is a key link in the AF occurrence. It should be noted that chronic inflammation is not only associated with AF, but also predisposes to the development of thromboembolic complications of arrhythmia [10, 14].

Thus, inflammatory markers are involved in the AF pathogenesis, and the situation with chronic inflammation becomes even more significant when AF is combined with CMS. According to Packer, "atrial cardiomyopathy associated with inflammation" can lead to the development of "atrial fibrillation associated with inflammation" [14].

Study limitations. One of the limitations of this study is the effect of drug therapy, in particular, drugs from the group of statins, on the systemic inflammatory process, and currently it is not possible to assess pro-inflammatory biomarkers in patients without therapy, but in the long term, with a larger data set, such an additional analysis is necessary. Also, a single-stage examination of patients with AF and CMS does not allow to fully study the possible clinical role of inflammatory biomarkers on AF course and treatment tactics, so prospective observation and study of the clinical significance of determining the level of pro-inflammatory biomarkers in patients with CMS and AF are required.

Conclusion

1. The concentration in blood plasma of IL-6, in blood serum of CRP and TNF-α in patients with AF in combination with CMS is higher than in patients with AF without CMS, and higher than in patients with CMS without arrhythmia.
2. TEF in patients with AF in combination with CMS is greater than in patients with AF without CMS, and more than in patients with CMS without arrhythmia.
3. The indices of LP and PP volumes in patients with AF in combination with CMS are higher than in patients with AF without CMS.
4. Correlations were established between inflammatory markers and indicators characterizing visceral obesity, while the IL-6 and CRP concentrations in blood correlated with WC and TEF, and the TNF-α concentration in blood correlated only with TEF.
5. TEF has a greater effect on the IL-6 concentration, CRP, and TNF-α circulating in blood than other indicators that characterize obesity, such as BMI and WC.

Relationships and Activities: none.

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International register “Dynamics analysis of comorbidities in SARS-CoV-2 survivors” (AKTIV) and the register “Analysis of hospitalizations of comorbid patients infected during the second wave of SARS-CoV-2 outbreak” (AKTIV 2)

Arutyunov G. P., Tarlovskaya E. I., Arutyunov A. G., Belenkov Y. N., Konradi A. O., Lopatin Y. M., Rebrov A. P., Tereshchenko S. N., Chesnikova A. I., Hayrapetyan H. G., Babin A. P., Bakulin I. G., Bakulina N. V., Balykova L. A., Blagonravova A. S., Boldina M. V., Vaisberg A. R., Galyavich A. S., Gomonova V. V., Grigorieva N. U., Gubareva I. V., Demko I. V., Evzerikhina A. V., Zharkov A. V., Kamilova U. K., Kim Z. F., Kuznetsova T. Yu., Lareva N. V., Makarova E. V., Malchikova S. V., Nedogoda S. V., Petrova M. M., Pochinka I. G., Protasov K. V., Protsenko D. N., Ruzanov D. Yu., Sayganov S. A., Sarybaev A. Sh., Selezneva N. M., Sugraliev A. B., Fomin I. V., Khlynova O. V., Chizhova O. Yu., Shaposhnik I. I., Schukarev D. A., Abdrahmanova A. K., Avetisian S. A., Avoyan H. G., Azarian K. K., Aimakhanova G. T., Ayipova D. A., Akunov A. Ch., Alieva M. K., Aparkina A. V., Aruslanova O. R., Ashina E. Yu., Badina O. Y., Barisheva O. Yu., Batchayeva A. S., Bitieva A. M., Bikhteyev I. U., Borodulina N. A., Bragin M. V., Budu A. M., Burygina L. A., Bykova G. A., Varlamova D. D., Vezikova N. N., Verbitskaya E. A., Vilkova O. E., Vinnikova E. A., Vustina V. V., Galova E. A., Genkel V. V., Gorshenina E. I., Gostishev R. V., Grigorieva E. V., Gubareva E. Yu., Dabylova G. M., Demchenko A. I., Dolgikh O. Yu., Duvanov I. A., Duyshobayev M. Y., Evdokimov D. S., Egorova K. E., Ermilova A. N., Zheldybayeva A. E., Zarechnova N. V., Ivanova S. Yu., Ivanchenko E. Yu., Ilina M. V., Kazakovtseva M. V., Kazymova E. V., Kalinina Yu. S., Kamardina N. A., Karachenova A. M., Karetnikov I. A., Karoli N. A., Karpov O. V., Karsiev M. Kh., Kaskaeva D. S., Kasymova K. F., Kerimbekova Zh. B., Kerimova A. Sh., Kim E. S., Kiseleva N. V., Klimenko D. A., Klimova A. V., Kovalishena O. V., Kolmakova E. V., Kolchinskaya T. P., Kolyadich M. I., Kondriakova O. V., Konoval M. P., Konstantinov D. Yu., Konstantinova E. A., Kordukova V. A., Koroleva E. V., Kraposhina A. Yu., Kriukova T. V., Kuznetsova A. S., Kuzmina T. Y., Kuzmichev K. V., Kulchoroeva Ch. K., Kuprina T. V., Kouranova I. M., Kurenkova L. V., Kurchugina N. Yu., Kushubakova N. A., Levankova V. I., Levin M. E., Lyubavina N. A., Magdeyeva N. A., Mazalov K. V., Majseenko V. I., Makarova A. S., Maripov A. M., Marusina A. A., Melnikov E. S., Moiseenko N. B., Muradova F. N., Muradyan R. G., Musaelian Sh. N., Nikitina N. M., Ogurlieva B. B., Odegova A. A., Omarova Yu. M., Omurzakova N. A., Ospanova Sh. O., Pahomova E. V., Petrov L. D., Plastinina S. S., Pogrebetskaya V. A., Polyakov D. S., Ponomarenko E. V., Popova L. L., Prokofeva N. A., Pudova I. A., Rakov N. A., Rakhimov A. N., Rozanova N. A., Serikbolkyzy S., Simonov A. A., Skachkova V. V., Smirnova L. A., Soloveva D. V., Soloveva I. A., Sokhova F. M., Subbotin A. K., Sukhomlinova I. M., Sushilova A. G., Tagayeva D. R., Titojkina Yu. V., Tikhonova E. P., Tokmin D. S., Torgunakova M. S., Trenogina K. V., Trostianetckaia N. A., Trofimov D. A., Tulichev A. A., Tupitsin D. I., Tursunova A. T., Tiurin A. A., Ulanova N. D., Fatenkov O. V., Fedorishina O. V., Fil T. S., Fomina I. Yu., Fominova I. S., Frolova I. A., Tsvinger S. M., Tsoma V. V., Cholponbaeva M. B., Chudinovskikh T. I., Shakhgildyan L. D., Shevchenko O. A., Sheshina T. V., Shishkina E. A., Shishkov K. Yu., Sherbakov S. Y., Yausheva E. A.

The organizer of the registers "Dynamics analysis of comorbidities in SARS-CoV-2 survivors" (AKTIV) and "Analysis of hospitalizations of comorbid patients infected during the second wave of SARS-CoV-2 outbreak" (AKTIV 2) is the Eurasian Association of Therapists (EAT). Currently, there are no clinical registries in the Eurasian region designed to collect and analyze information on long-term outcomes of COVID-19 survivors with comorbid conditions. The aim of the register is to assess the impact of a novel coronavirus infection on long-term course of chronic non-communicable diseases 3, 6, 12 months after recovery, as well as to obtain information on the effect of comorbidity on the severity of COVID-19. Analysis of hospitalized patients of a possible second wave is planned for register "AKTIV 2". To achieve this goal, the register will include men and women over 18 years of age diagnosed with COVID-19 who are treated in a hospital or in outpatient basis. The register includes 25 centers in 5 federal districts of the Russian Federation, centers in the Republic of Armenia, the Republic of Kazakhstan, the Republic of Kyrgyzstan, the Republic of Belarus, the Republic of Moldova, and the Republic of Uzbekistan. The estimated capacity of the register is 5400 patients.

Keywords: SARS-CoV-2, registry, COVID-19, comorbidity, risk, multimorbidity.

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Arutyunov G. P.* ORCID: 0000-0002-6645-2515, Tarlovskaya E. I. ORCID: 0000-0002-9659-7010, Arutyunov A. G. ORCID: 0000-0003-1180-3549, Belenkov Y. N. ORCID: 0000-0002-6180-2619, Konradi A. O. ORCID: 0000-0001-8169-7812, Lopatin Y. M. ORCID: 0000-0003-1943-1137, Rebrov A. P. ORCID: 0000-0002-3463-7734, Tereshchenko S. N. ORCID: 0000-0001-9234-6129, Chesnikova A. I. ORCID: 0000-0002-9323-592X, Hayrapetyan H. G. ORCID: 0000-0002-8764-5623, Babin A. P. ORCID: none, Bakulin I. G. ORCID: 0000-0002-6151-2021, Bakulina N. V. ORCID: 0000-0003-4075-4096, Balykova L. A. ORCID: 0000-0002-2290-0013, Blagonravova A. S. ORCID: 0000-0002-1467-049X, Boldina M. V. ORCID: 0000-0002-1794-0707, Vaisberg A. R. ORCID: 0000-0003-3658-5330, Galyavich A. S. ORCID: 0000-0002-4510-6197, Gomonova V. V. ORCID: 0000-0002-9816-9896, Grigorieva N. U. ORCID: 0000-0001-6795-7884, Gubareva I. V. ORCID: 0000-0003-1881-024X, Demko I. V. ORCID: 0000-0001-8982-5292, Evzerikhina A. V. ORCID: none, Zharkov A. V. ORCID: 0000-0001-6649-0928, Kamilova U. K. ORCID: 0000-0002-5104-456X, Kim Z. F. ORCID: 0000-0003-4240-3329, Kuznetsova T. Yu. ORCID: 0000-0002-6654-1382, Lareva N. V. ORCID: 0000-0001-9498-9216, Makarova E. V. ORCID: 0000-0003-4394-0687, Malchikova S. V. ORCID: 0000-0002-2209-9457, Nedogoda S. V. ORCID: 0000-0001-5981-1754, Petrova M. M. ORCID: 0000-0002-8493-0058, Pochinka I. G. ORCID: 0000-0001-5709-0703, Protasov K. V. ORCID: 0000-0002-6516-3180, Protsenko D. N. ORCID: 0000-0002-5166-3280, Ruzanov D. Yu. ORCID: 0000-0001-5291-4937, Sayganov S. A. ORCID: 0000-0001-7319-2734, Sarybaev A. Sh. ORCID: 0000-0003-2172-9776, Selezneva N. M. ORCID: 0000-0002-3004-2063, Sugraliev A. B. ORCID: 0000-0002-8255-4159, Fomin I. V. ORCID: 0000-0003-0258-5279, Khlynova O. V. ORCID: 0000-0003-4860-0112, Chizhova O. Yu. ORCID: 0000-0002-1716-7654, Shaposhnik I. I. ORCID: 0000-0002-7731-7730, Schukarev D. A. ORCID: none, Abdrahmanova A. K. ORCID: 0000-0002-6332-9503, Avetisian S. A. ORCID: none, Avoyan H. G. ORCID: 0000-0002-3335-7255, Azarian K. K. ORCID: none, Aimakhanova G. T. ORCID: none, Ayipova D. A. ORCID: none, Akunov A. Ch. ORCID: none, Alieva M. K. ORCID: 0000-0002-0763-6111, Aparkina A. V. ORCID: 0000-0001-8463-2379, Aruslanova O. R. ORCID: 0000-0002-6974-2614, Ashina E. Yu. ORCID: 0000-0002-7460-2747, Badina O. Y. ORCID: 0000-0001-9068-8088, Barisheva O. Yu. ORCID: 0000-0001-6317-1243, Batchayeva A. S. ORCID: none, Bitieva A. M. ORCID: 0000-0002-5383-2367, Bikhteyev I. U. ORCID: 0000-0003-0663-3549, Borodulina N. A. ORCID: 0000-0003-1107-5772, Bragin M. V. ORCID: 0000-0003-2308-4887, Budu A. M. ORCID: none, Burygina L. A. ORCID: 0000-0002-2613-8783, Bykova G. A. ORCID: 0000-0003-0823-4605, Varlamova D. D. ORCID: 0000-0002-4015-5109, Vezikova N. N. ORCID: 0000-0002-8901-3363, Verbitskaya E. A. ORCID: 0000-0002-5710-7082, Vilkova O. E. ORCID: 0000-0002-1129-7511, Vinnikova E. A. ORCID: 0000-0002-5948-1561, Vustina V. V. ORCID: 0000-0003-1466-285X, Galova E. A. ORCID: 0000-0002-9574-2933, Genkel V. V. ORCID: 0000-0001-5902-3803, Gorshenina E. I. ORCID: none, Gostishev R. V. ORCID: 0000-0002-2379-5761, Grigorieva E. V. ORCID: 0000-0001-6064-560X, Gubareva E. Yu. ORCID: 0000-0001-6824-3963, Dabylova G. M. ORCID: none, Demchenko A. I. ORCID: none, Dolgikh O. Yu. ORCID: none, Duvanov I. A. ORCID: 0000-0003-0789-429X, Duyshobayev M. Y. ORCID: none, Evdokimov D. S. ORCID: 0000-0002-3107-1691, Egorova K. E. ORCID: 0000-0003-4233-3906, Ermilova A. N. ORCID: 0000-0002-5704-697X, Zheldybayeva A. E. ORCID: none, Zarechnova N. V. ORCID: none, Ivanova S. Yu. ORCID: 0000-0002-0720-6621, Ivanchenko E. Yu. ORCID: 0000-0003-4506-1053, Ilina M. V. ORCID: 0000-0003-2566-1086, Kazakovtseva M. V. ORCID: 0000-0002-0981-3601, Kazymova E. V. ORCID: none, Kalinina Yu. S. ORCID: 0000-0001-6037-5857, Karachenova A. M. ORCID: 0000-0003-1704-490X, Karetnikov I. A. ORCID: 0000-0002-0922-6925, Karoli N. A. ORCID: 0000-0002-7464-826X, Karpov O. V. ORCID: 0000-0001-7909-0675, Karsiev M. Kh. ORCID: 0000-0002-1794-0694, Kaskaeva D. S. ORCID: 0000-0002-0794-2530, Kasymova K. F. ORCID: 0000-0001-8448-6113, Kerimbekova Zh. B. ORCID: none, Kerimova A. Sh. ORCID: 0000-0002-2806-5901, Kim E. S. ORCID: none, Kiseleva N. V. ORCID: 0000-0002-0935-8717, Klimenko D. A.

ORCID: none, Klimova A.V. ORCID: 0000-0002-3176-7699, Kovalishena O.V. ORCID: 0000-0002-9595-547X, Kolmakova E.V. ORCID: none, Kolchinskaya T.P. ORCID: none, Kolyadich M.I. ORCID: 0000-0002-0168-1480, Kondriakova O.V. ORCID: 0000-0002-4092-6612, Konoval M.P. ORCID: 0000-0002-8187-6105, Konstantinov D.Yu. ORCID: 0000-0002-6177-8487, Konstantinova E.A. ORCID: 0000-0002-6022-0983, Kordukova V.A. ORCID: none, Koroleva E.V. ORCID: none, Kraposhina A.Yu. ORCID: 0000-0001-6896-877X, Kriukova T.V. ORCID: none, Kuzmina T.Y. ORCID: 0000-0002-0105-6642, Kuzmichev K.V. ORCID: none, Kulchoroeva Ch.K. ORCID: 0000-0003-2801-1994, Kuprina T.V. ORCID: 0000-0002-1176-7309, Kouranova I.M. ORCID: none, Kurenkova L.V. ORCID: none, Kurchugina N.Yu. ORCID: 0000-0003-2988-7402, Kushubakova N.A. ORCID: 0000-0001-6874-7125, Levankova V.I. ORCID: 0000-0002-0788-4449, Levin M.E. ORCID: 0000-0002-9197-1691, Lyubavina N.A. ORCID: 0000-0002-8914-8268, Magdeyeva N.A. ORCID: 0000-0002-6397-3542, Mazalov K.V. ORCID: none, Majseenko V.I. ORCID: 0000-0003-2133-4360, Makarova A.S. ORCID: 0000-0002-0486-9657, Maripov A.M. ORCID: 0000-0003-2801-1994, Marusina A.A. ORCID: 0000-0002-5301-5746, Melnikov E.S. ORCID: 0000-0002-8521-6542, Moiseenko N.B. ORCID: 0000-0003-2072-6370, Muradova F.N. ORCID: 0000-0002-2723-8081, Muradyan R.G. ORCID: none, Musaelian Sh.N. ORCID: none, Nikitina N.M. ORCID: 0000-0002-0313-1191, Ogurlieva B.B. ORCID: none, Odegova A.A. ORCID: 0000-0001-9691-6969, Omarova Yu.M. ORCID: 0000-0002-0942-6070, Omurzakova N.A. ORCID: 0000-0003-3970-9706, Ospanova Sh.O. ORCID: none, Pahomova E.V. ORCID: 0000-0002-8335-4626, Petrov L.D. ORCID: none, Plastinina S.S. ORCID: 0000-0002-0534-5986, Pogrebetskaya V.A. ORCID: none, Polyakov D.S. ORCID: 0000-0001-8421-0168, Ponomarenko E.V. ORCID: none, Popova L.L. ORCID: 0000-0003-0549-361X, Prokofeva N.A. ORCID: 0000-0002-7679-413X, Pudova I.A. ORCID: none, Rakov N.A. ORCID: none, Rakhimov A.N. ORCID: none, Rozanova N.A. ORCID: none, Serikbolkyzy S. ORCID: none, Simonov A.A. ORCID: 0000-0002-7915-3880, Skachkova V.V. 0000-0001-7512-2414, Smirnova L.A. ORCID: 0000-0002-2083-0373, Soloveva D.V. ORCID: 0000-0001-5695-0433, Soloveva I.A. ORCID: 0000-0002-1999-9534, Sokhova F.M. ORCID: 0000-0002-6208-2908, Subbotin A.K. ORCID: none, Sukhomlinova I.M. ORCID: none, Sushilova A.G. ORCID: 0000-0002-7277-5046, Tagayeva D.R. ORCID: none, Titojkina Yu.V. ORCID: 0000-0001-9974-359X, Tikhonova E.P. ORCID: 0000-0001-6466-9609, Tokmin D.S. ORCID: none, Torgunakova M.S. ORCID: 0000-0002-5483-0048, Trenogina K.V. ORCID: 0000-0002-4137-5533, Trostianetckaia N.A. ORCID: none, Trofimov D.A. ORCID: 0000-0001-7613-7132, Tulichev A.A. ORCID: 0000-0002-3157-2218, Tupitsin D.I. ORCID: none, Tursunova A.T. ORCID: none, Tiurin A.A. ORCID: none, Ulanova N.D. ORCID: 0000-0002-5107-6051, Fatenkov O.V. ORCID: 0000-0002-4928-5989, Fedorishina O.V. ORCID: 0000-0002-0155-676X, Fil T.S. ORCID: none, Fomina I.Yu. ORCID: none, Fominova I.S. ORCID: none, Frolova I.A. ORCID: none, Tsvinger S.M. ORCID: 0000-0003-2082-9839, Tsoma V.V. ORCID: 0000-0002-0662-1217, Cholponbaeva M.B. ORCID: none, Chudinovskikh T.I. ORCID: 0000-0002-7515-2215, Shakhgildyan L.D. ORCID: 0000-0003-3302-4757, Shevchenko O.A. ORCID: none, Sheshina T.V. ORCID: none, Shishkina E.A. ORCID: 0000-0001-6965-7869, Shishkov K.Yu. ORCID: 0000-0003-2942-6200, Sherbakov S.Y. ORCID: none, Yausheva E.A. ORCID: none.

*Corresponding author: arut@ossn.ru

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The organizer of the registers "Dynamics analysis of comorbidities in SARS-CoV-2 survivors" (AKTIV) and "Analysis of hospitalizations of comorbid patients infected **during the second wave** of SARS-CoV-2 outbreak" (AKTIV 2) is the Eurasian Association of Therapists (EAT). EAT experts believe that the impact of a new coronavirus infection caused by SARS-CoV-2 (COVID-19) on the course of comorbid conditions in the long-term period is becoming topical issues for public health. The absence of population immunity, the rapid virus spread, the relatively high frequency of severe disease forms (~10-20% of cases, especially in the elderly with concomitant diseases), the multiple organ nature of the damage, the severity of systemic inflammatory reaction, the presence of a local vascular lesion, with predominant damage to the microcirculatory bloodstream vessels, suggest that SARS-CoV-2 can increase the likelihood of progression of the existing concomitant pathology. Currently, there are no clinical registries in the Eurasian region designed to collect and analyze information on long-term outcomes of COVID-19 survivors with comorbid conditions. The creation of a register to assess the COVID-19 impact on dynamics of chronic non-communicable diseases in the long-term period is an important scientific and practical work.

The main task of the ACTIV registry is to obtain information on the effect of comorbidity on the COVID-19 severity and to assess the dynamics of comorbid conditions in patients who have come through COVID-19, 3, 6, 12 months after recovery (discharge from the hospital or discharge after outpatient treatment). Additionally, at the time of ACTIV creation, it was not clear whether there would be a second wave of the pandemic, but experts assumed a high probability of such an event. Therefore, the question came up: "will the risk factors of infection, the distribution of phenotypes of patients and the outcomes of the disease in the hospitalized patients of the first wave and second wave differ"? Analysis of hospitalized patients of a possible second wave is planned for register ACTIV 2.

The ACTIV register will include both hospitalized patients and those receiving outpatient treatment. When filling out the ACTIV register, the following important information will be received:

- newly emerged non-communicable, infectious and oncological diseases (follow-up period: 12 months from the moment of seeking medical help for COVID-19);
- severity dynamics of pre-existing chronic diseases (follow-up period: 12 months from the moment of seeking medical help for COVID-19);

Table 1

Design of register ACTIV SARS-CoV-2

N	Visits	Outpatient branch of the Register	Hospital branch of the Register
1	Enrollment	Retrospective data from outpatient medical record	Retrospective data from medical history
2	7-12 days	Retrospective data from outpatient medical record	Retrospective data from medical history
3	Exodus (discharge/death)	Retrospective data from outpatient medical record	Retrospective data from medical history
4	3 months after discharge	Phone call	Phone call
5	6 months after discharge	Phone call	Phone call
6	12 months after discharge	Phone call	Phone call

• dynamics of traditional risk factors: total cholesterol, low-density lipoprotein cholesterol, triglycerides, blood glucose, blood pressure, body mass index (follow-up period: 12 months after seeking medical help for COVID-19);

• Severity of COVID-19, depending on pre-existing diseases and risk factors for major non-communicable diseases;

• occurrence of new cases of disability/change in the disability degree (follow-up period: 12 months after seeking medical help for COVID-19);

• frequency of deaths (follow-up period: 12 months after seeking medical help for COVID-19).

Patient population. The register will include men and women over the age of 18 with COVID-19 diagnosis with the preservation of anonymity (data from the swab analysis of the nasopharynx and oropharynx, antibody titer, a typical picture according to computed tomography), who are being treated in a hospital or receiving treatment at home.

Territory of register execution. The register includes 25 centers in 5 federal districts of the Russian Federation, centers in the Republic of Armenia, the Republic of Kazakhstan, the Republic of Kyrgyzstan, the Republic of Belarus, the Republic of Moldova, and the Republic of Uzbekistan. The estimated capacity of the registry is not less than 5400 patients.

Definitions. Chronic non-communicable diseases were determined in accordance with current clinical guidelines. A multimorbid patient was considered to have 2 or more verified diseases and received treatment for these diseases.

Study design. Study design: multicenter registry with two disjoint branches (outpatient branch and hospital branch). Both branches of the register have 6 visits (Table 1). The follow-up duration is 12 months. It is planned to analyze the patient's medical examination data (the primary document is medical history or outpatient card) and the data obtained by telephone surveys using a standard questionnaire 3, 6, 12 months after recovery from COVID-19.

Register organization. Start of patient recruitment on June 29, 2020, end of recruitment on November 29, 2020. Completion of the register on November 29, 2021. 3 committees organize and control the register work: the organizing committee, the supervisory committee, and the committee for analysis of endpoints and control of filling out individual registration cards (IRC). IRC and document management are only electronic. The register is formed by 140 doctors in 25 centers. Each IRC passes monitor control.

Ethical review. The ethical review was carried out by the Pirogov Russian National Research Medical University Ethics Committee for centers in the Russian Federation and local ethics committees in other countries participating in the register. Register registration: ID ClinicalTrials.gov: NCT04492384.

Register's website. Information on the Register is available on the website of the Eurasian Association of Therapists or by direct link: https://ACTIV.euat.ru, available from fixed and mobile devices.

Data collection. If the patient meets the enrollment criteria (see the section "Patient population"), he is included in one of the register branches: either outpatient or hospital. A depersonalized IRC is filled in for the patient with fixing subsequent dates of patient's visits. All information received about the patient, according to the rules of quality clinical practice, is confidential, only the automatically assigned unique number (identifier) of the patient is entered in IRC.

ACTIV 2 register

The ACTIV 2 register purpose: to study the differences in populations, comorbidities, and treatment regimens obtained during a statistical comparison of the main indicators of ACTIV and ACTIV 2 in patients during the hospital period.

Patient population. The register will include men and women with COVID-19 over 18 years of age with the preservation of anonymity (data from the swab analysis of the nasopharynx and oropharynx, antibody titer, a typical picture according to

Table 2

Registers with follow-up period of 1 year or more

Register name (No. in article bibliography)	Number of patients/ follow-up period (years)	Register's goal
Cardiopulmonary Inflammation and Multi-System Imaging During the Clinical Course of COVID-19 Infection in Asymptomatic and Symptomatic Persons	180/1	To understand how the COVID-19 virus causes wide differences in how sick one can become from the infection.
A Longitudinal Study of COVID-19 Sequelae and Immunity	900/3	To learn about any long-term medical problems that people who have recovered from COVID-19 might have, and whether they develop an immune response to SARS-CoV-2 that provides protection against reinfection.
Austrian COVID-19 Registry	1000/2	The AGMT-COVID-19 Registry is designed as multicenter observational cohort of patients, that are tested positive for SARS-CoV-2. Data will be collected from all sites in Austria willing to participate. Due to the non-interventional nature of the AGMT_COVID-19 registry, only routine data, which has already been recorded in the patient's medical chart, is transferred to the eCRF.
Prospective Hospital Registry of Patients With Suspected or Confirmed Coronavirus Infection (COVID-19) and Community-acquired Pneumonia (TARGET-VIP)	1124/2	A prospective medical registry of such patients (confirmed or suspected severe COVID-19 or community-acquired pneumonia), hospitalized to National Medical and Surgical Center, is intended to analyze and compare their clinical and instrumental data, co-morbidity, treatment, short-term and long-term outcomes in real clinical practice.
COVID-19 Recovered Volunteer Research Participant Pool Registry	10000/20	This is a prospective observational registry of COVID-19 recovered patients who are no longer symptomatic. This Registry is intended to serve as a pool of individuals that can participate in studies associated with serological testing, characterization of immunity and immune response, vaccine development, and convalescent plasma donors.
Natural History of Post-Coronavirus Disease 19 Convalescence at the National Institutes of Health	1200/3	In this study, researchers will use survey data to describe the different ways people experience and recover from COVID-19. They will also use the data to help create future studies to understand why some people do not fully recover.
The McMaster Multi-Regional COVID-19 Hospital Case Registry (COREG)	1500/1	The McMaster Multi-Regional Hospital Coronavirus Registry (COREG) is a platform that is collecting detailed case data on laboratory confirmed COVID-19 hospital inpatients and outpatients. The COREG platform will provide rapid high-quality evidence to improve the prevention and clinical management of COVID-19 for older adults in Canada, and internationally. The COREG platform will also provide researchers and partners with complete regional level clinical data on COVID-19 cases to inform rapid decision-making and projections, sub-studies, extensions, and linkage for all affected populations.
COVID-19 Survivorship Registry	350/1	The objectives for this study include providing structural and function information about lung and heart using chest imaging, MRI, Echo, Spirometry, and blood markers in order to assess severity of cardiopulmonary injury and short- and long-term sequelae of COVID-19 infection as well as assess indicators of mental health and quality of life.
Innovative Support for Patients With SARS-COV2 Infections (COVID-19) Registry (INSPIRE)	4800/1,5	This study will use a digital platform to longitudinally track comprehensive information including patient self-report as well as data that describe the process and outcome of care in the electronic medical record (EMR) of a large representative sample of patients under investigation for SARSCOV2.

Table 2. Continuation

Register name (No. in article bibliography)	Number of patients/ follow-up period (years)	Register's goal
Behavior, Environment And Treatments for Covid-19 (BEAT19)	100000/1	The purpose of this study is to understand at the population level the symptomatic course of known or suspected COVID-19 patients while sheltering-in-place or under quarantine. Symptoms will be measured using a daily report derived from the CTCAE-PRO as well as free response. Outcomes will be assessed based on the duration and severity of infection, hospitalization, lost-to-follow-up, or death. As a patient-centric registry, patients themselves may propose, suggest, and/or submit evidence or ideas for relevant collection.
Analysis of Chronic Non-infectious Diseases Dynamics After COVID-19 Infection in Adult Patients (ACTIV)	5400/1	Non-commercial depersonalized multi-centered registry study on analysis of chronic non-infectious diseases dynamics after SARS-CoV-2 infection in cohort of Russian adult patients. Retrospective analysis of medical histories and outcomes in adults with pre-existing conditions after SARS-CoV-2 infection and prospective monitoring of health status during 3, 6 and 12 months after discharge. Comorbidities worsening risk factors measuring through evaluation of range of indicators such as dynamics of diabetes, CKD, COPD, bronchial asthma, incidence of hypertonic crises, vascular events and others.

computed tomography) who are being treated in a hospital in the period from October 01, 2020.

Territory of register execution. Register implementation territory — 18 centers in 5 federal districts of the Russian Federation and in the Republic of Belarus. The estimated register capacity is 2500 patients.

Study design. Multicenter register. The follow-up duration — the hospital stay time. Analyzing the history and outcome of the disease retrospectively is planned.

Register organization. Patient recruitment starts on October 01, 2020, and ends on March 30, 2021.

Register registration: ID ClinicalTrials.gov: NCT04709120.

Register's website. Information on the Register is available on the website of the Eurasian Association of Therapists or by direct link: https://ACTIV.euat.ru, available from fixed and mobile devices.

Methods of statistical analysis of registers ACTIV and ACTIV 2. Data processing within the register will be performed using the IBM SPSS Statistics 25 statistical package. The work will be carried out in several stages.

Stage 1. Data preparation. The main stage 1 is the cleaning of quantitative follow-up (results of laboratory and instrumental diagnostics, drug dosages, etc.) from input errors and the use of different scales (for example, ng/ml, mcg/ml, mcg/l for the D-dimer). During this stage, new features will also be constructed, such as presence of specific polymorbidity variants of interest, presence of significant negative dynamics of individual indicators (computed tomography data, D-dimer and C-reactive protein), and calculation of combined variables (body mass index, glomerular filtration rate, etc.). Finally, for the purposes of modeling and clustering (stage 4), the quantitative variables will be regularized by the Z-scaling method.

Stage 2. Exploratory analysis. First of all, the quantitative variables will be checked for normality using the Shapiro-Wilk agreement test (p=0,05) and graphical analysis. The vast majority of numeric variables do not have a normal distribution, so stage 3 (see below) will be implemented primarily using nonparametric tests.

Using logistic regression (first one-factor, then multi-factor by step-by-step construction), the variables that most significantly affect the outcomes of interest (mortality rate, artificial ventilation transfer, cytokine storm development, etc.) will be identified.

Finally, to avoid multicollinearity and incorrect interpretation of relationships, correlation matrices and multi-input frequency tables will be constructed. Based on these data and the results of logistic regression, the final hypothesis adjustment within the register will be carried out.

Stage 3. Hypothesis testing. The vast majority of hypotheses will be tested using nonparametric criteria:

• Hypotheses about relationship of quantitative variables-using the Pearson rank correlation;

• Hypotheses about difference in quantitative indicators of the groups of interest (clinical parameters, degree of oxygenation) — using the Craskell-Wallis test/Mann-Whitney test;

• Hypotheses about different frequency of events in the groups (mortality rate, hospitalization, etc.) — using the Pearson Chi-Square test. In 2×2 groups with a small number of follows-up — using the Yates continuity correction.

The odds ratio will be calculated for all hypotheses. In a number of cases, the odds ratio was adjusted for significant concomitant factors identified in stage 2: age, number of diseases in anamnesis, and so on, using multivariate logistic regression.

All hypotheses were tested at a significance level of p=0,05. A posteriori inter-group comparisons were performed using the Bonferroni correction.

Stage 4. Modeling and clustering. At the final stage of the register, the following is planned:

A) Modeling of adverse patient outcomes: logistic regression by step-up method with control of predictor collinearity and iterative construction (bagging).

B) Clustering of patients by demographic (gender-age) parameters and anamnesis (concurrent diseases) with further comparison of outcomes between clusters: "phenotyping" of patients who have been infected with SARS-CoV-2. It is planned to use both the K-means method and hierarchical clustering methods.

Discussion

Over the past 20 years, four major outbreaks of viral infectious diseases have caused a large number of deaths worldwide: SARS, H1N1 influenza, MERS, and COVID-19. All of them are initially clinically manifested as upper and lower respiratory tract infections, but can progress to multiple organ failure [1]. In a study by Chu KH, et al., the long-term effect of SARS infection on kidney function was studied: among 536 patients with SARS, 36 (6,7%) developed impaired renal function, which was manifested on average 20 days (range of 5-48 days) after the onset of viral infection, despite the initial normal plasma creatinine level [2]. According to a study by Wu Q, et al, patients who had recovered from SARS-CoV, disorders of lipid and glucose metabolism with elevated levels of phosphatidylinositol and lysophosphatidylinositol were found [3]. Another study by Yang JK, et al. shown that SARS coronavirus can cause damage to the kidneys, heart, lungs, and endocrine part of the pancreas [4]. In a study by Leow MK, et al., 39,3% of patients showed signs of hypocorticism out of 61 patients who had SARS-CoV. Dysfunction of hypothalamus-pituitary-adrenal axis in the majority was resolved within a year. Two (3,3%) of the cohort of patients with hypocorticism had transient subclinical thyrotoxicosis, and four (6,7%) had biochemical hypothyroidism [5]. There are a small number of studies analyzing the damage to the cardiovascular system as a result of SARS-CoV-1 and MERS infections. This is how acute coronary syndrome, transient diastolic dysfunction, hypotension, bradycardia, and transient cardiomegaly are described [6-11]. Thus, the problem of long-term changes in patients who have been infected with coronaviruses becomes an urgent problem of modern medicine, the study of which, undeniably, should begin with registers.

According to the site Trials.gov, there are currently 91 registries in the world dedicated to analysis of patients with COVID-19. The registers classification is a complex and difficult task, but it is necessary in order to know what clinically significant questions we can expect answers in the near future. It seems appropriate to divide the registers according to the following principle: ***those studying the course*** of ***COVID-19 in special patient populations*** (patients with oncological diseases [12], patients with chronic obstructive pulmonary disease [13], patients with onco-hematological diseases [14], patients with rheumatological diseases [15] and patients with cardiovascular diseases [16]); ***those studying complications recorded in patients with COVID-19*** (pulmonary artery thromboembolia [17], myocarditis [18], cardiac arrhythmias [19], with acute heart failure [20], with arterial and venous thrombosis [21]); ***studying the effect of individual drugs and effects on the course of COVID-19*** (aerobic exercise [22], various drug therapy regimens [23]); ***studying the changes in patients who have come through COVID-19*** (state of immune system [24], quality of life [25]).

A separate type of registry consists of studies that assess the clinical condition dynamics of polymorbid patients who have come through COVID-19. Without disputing the value for real practice of the data that are planned to be obtained in short-term registers lasting up to 1 year [26] and small (up to 1 thousand patients [27]), from 1 thousand to 3 thousand patients [28] — we believe that the initial versatility of polymorbid patients and difficulties in assessing the initial state dynamics require both a larger number of patients (for example, assuming the inclusion of >5 thousand patients) and longer follow-up periods (Table 2). Register ACTIV, presented by us, is an international one, including data on patients from 7 countries of the Eurasian region, and is designed to

include at least 5400 patients whose status severity required either hospitalization or allowed the patient to be left for outpatient treatment. Within the register, prospective follow-up of patients is planned for a year, while the possibility of extending the study remains with the appropriate decision of the supervisory committee. The publication of data obtained during the follow-up of patients for 12 months is mandatory. Such indicators as the need for emergency and planned medical treatment, the need for hospitalization, the occurrence of disability, the analysis of comorbid disease course, the incidence of non-communicable diseases (for example, myocardial infarction, stroke, diabetes mellitus, decompensation of heart failure) will be assessed, which will allow to form an idea of the dynamics of existing chronic diseases and assess the prognosis of these patients in post-COVID-19 period. For comparison, the COVID-19 Recovered Volunteer Research Participant Pool Registry (USA) [29] provides only periodic serological test of recovered patients. The Behavior, Environment And Treatments for Covid-19 (BEAT19) register (USA) [30] suggests follow-up only for non-hospitalized patients with COVID-19. The Innovative Support for Patients With SARS-COV2 Infections (COVID-19) Registry (INSPIRE) (USA) [31], which is expected to include 4800 patients, is supposed to analyze the incidence of myalgic encephalomyelitis/chronic fatigue syndrome, as well as the frequency of outpatient and inpatient medical care and mortality, but does not provide an analysis of comorbid disease course and non-communicable disease incidence. Equally important is the issue: does the course of COVID-19 during the first wave (spring — early autumn 2020) differ from the second wave (autumn-winter 2020-2021)? The ACTIV 2 register is devoted to clinical features comparison of disease course during the first and second waves in hospitalized patients.

Thus, in order to optimize the treatment process in real practice, fundamentally new information obtained during long-term prospective follow-up of patients who have come through SARS-CoV-2 is required. This task is the main one in international register ACTIV. Register ACTIV 2 will allow to compare the clinical course features of the first and second waves of COVID-19 in hospitalized patients.

Relationships and Activities: none.

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