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Predictors of myocardial fibrosis and loss of epicardial adipose tissue volume in the long-term period after myocardial infarction

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Aim. To assess the changes of biochemical markers in hospitalization, the relationship with the severity of myocardial fibrosis and the epicardial adipose tissue (EAT) thickness one year after myocardial infarction (MI).

Material and methods. A total of 88 patients (65 men and 23 women) with MI were examined. The percentage of cicatricial changes in the myocardium and the EAT thickness were measured using the magnetic resonance imaging (MRI) one year after MI. In the hospitalization (days 1 and 12) and 1 year after MI, the concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP), stimulating growth factor (ST2), interleukin-33 (IL-33) and type I collagen (COL-1). The data were analyzed using descriptive statistics, correlation and ROC analysis, and logistic regression (Statistica 9.0).

Results. One year after MI, cicatricial changes were detected in 68 (77%) patients: 27 people had myocardial fibrosis <5%, 22 patients — 5-15%, and 19 patients >15%. We established that myocardial fibrosis after MI is associated with unfavorable medical history, a complicated course during in-hospital period and higher concentrations of ST2, NT-proBNP, COL-1 compared with patients without myocardial fibrosis. High levels of ST2, NT-proBNP increase the risk of myocardial fibrosis by 1,2 and 1,8 times after hospitalization, respectively. In patients with myocardial fibrosis >15%, IL-33 level was significantly lower in the 1st day of MI. It was found that the EAT thickness increases with fibrosis of 5-15%. An increase in the left (LV) and right ventricular (RV) EAT thickness by 1,33 times and 1,34 times, respectively, increases the risk of myocardial fibrosis (LV EAT thickness, mm (OR 1,33; 95% CI (1,08-1,4), AUC 0,75; RV EAT thickness, mm (OR 1,34; 95% CI (1,15-1,43), AUC 0,79). In patients with myocardial fibrosis >15%, EAT thickness decreases and correlates with NT-proBNP increase in the acute period and a one year after MI.

Conclusion. The development of myocardial fibrosis one year after MI is associated with an increase in ST2, NT-proBNP, COL-1, both in the hospitalization and 1 year after MI. The decrease in IL-33 concentration during hospitalization with MI is accompanied by the development of fibrosis >15% of the myocardium.

Key words: epicardial adipose tissue, markers of myocardial fibrosis, markers of inflammation.

Relationships and Activities: not.

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Myocardial fibrosis is presented in many cardiovascular diseases (CVD), including coronary artery disease (CAD), hypertension and cardiomyopathy [1]. Myocardial fibrosis develops due to injury and impaired perfusion of myocardium, cardiomyocyte death, inflammation and, as a result, the intensive collagen synthesis. Irreversible structural and functional changes and ventricular remodeling are accompanied by a decrease in myocardial elasticity and contractility. As a result, the myocardium is not able to adequately circulate blood, which leads to heart failure (HF) and related manifestations, such as severe dyspnea, general weakness, edema, hepatomegaly, tissue hypoxia, and lung congestion [2]. Promising is the study of IL-33/ST2 role in fibrogenesis development. As a rule, the IL-33/ST2 signaling pathway has an anti-inflammatory/antiproliferative effect, but in chronic inflammation, it initiates sclerosis of impaired lungs, liver, and pancreas [3]. The role of IL-33/ST2 in cardiac fibrosis has not been studied. Meanwhile, IL-33/ST2 may be one of the cardiac fibrosis markers in the post-hospital period after myocardial infarction (MI).

An essential role in myocardial fibrosis is played by epicardial adipose tissue (EAT), which is located next to the myocardium and can secrete fibrogenic factors: pro-inflammatory cytokines and adipokines [4]. Adipokines and pro-inflammatory cytokines secreted by adipose tissue (AT) can affect myocardial metabolism, increase cardiomyocyte hypertrophy and death, and potentiate changes in the structure and composition of the extracellular matrix [5]. In turn, the myocardium synthesizes substances that regulate the metabolic activity of EAT, in particular, the natriuretic peptide, which activates lipolysis and thermogenesis in AT, increasing the transcription of proteins such as uncoupling protein 1 (UCP-1) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), limiting the AT gain [6].

The relationship between the severity of myocardial fibrosis and EAT volume after MI has not been studied previously. However, the study of parameters associated with cardiac fibrosis and EAT thickness can be both theoretically and practically significant for identifying early signs of cardiac fibrosis, monitoring of treatment and prognosis.

The aim of the study was to assess the changes of biochemical markers of fibrosis during hospitalization, its relationship with the severity of cardiac fibrosis and EAT thickness one year after ST-segment elevation MI (STEMI).

Material and methods

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The local medical ethics committee approved this study. All patients signed informed consent. The study included 88 patients (65 men and 23 women) with STEMI. The mean age of patients was 54,6 (47,7; 62,7) years. The diagnosis of MI was established according to the Russian Society of Cardiology criteria — typical chest pain lasting >15 minutes, electrocardiography changes (ECG, ST elevation in at least two leads) and laboratory parameters (increased levels of creatine phosphokinase (CPK) and CPK myocardial band (CPK-MB), troponin T). There were following exclusion criteria: age <45 and >80 years; severe comorbidities (cancer, infectious disease, mental disease, chronic obstructive pulmonary disease, connective tissue disease, kidney and liver failure, Killip class III-IV acute heart failure, carbohydrate metabolism disorders (impaired fasting glycemia, carbohydrate intolerance, diabetes)).

In all patients, primary percutaneous coronary intervention (PCI) of culprit artery was used as reperfusion therapy. During hospitalization (on average 12 days), β-blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics, nitrates, aspirin, heparin and clopidogrel were used with the same frequency in all studied groups.

Using an enzyme immunoassay, following parameters were determined in all patients on the 1st and 12th day of hospitalization and 1 year after MI: N-terminal pro-brain natriuretic peptide (NT-proBNP Biomedica, Slovakia), stimulating growth factor (Critical Diagnostics Presage® ST2 Assay kit, USA), interleukin-33 (eBiosciens Human IL-33 Platinum ELISA, USA) and type I collagen (Cloud-Clone Corp., USA).

Cardiac fibrosis was assessed by the percentage of myocardial scarring. One year after MI, patients underwent contrast-enhanced cardiac MRI using an ExelartAtlas 1.5 MRI scanner (Toshiba, Japan). We used a gadolinium-based paramagnetic contrast agent at a concentration of 0,5 mmol/ml. For visualization of cardiac fibrosis zones, which are areas of delayed washout of paramagnetic contrast agent, a delayed scan was performed 6 minutes after agent administration using T1 weighted image with the following parameters: time of echo (TE) — 24 ms, time of repeat (TR) — 1000 ms, flip angle (FA) — 90°, matrix — 256x256, slice thickness — 7 mm; short-axis left ventricular (LV) slice orientation was used. The obtained DICOM images were processed and analyzed using the Segment version 2.0 R 4265 software (Medviso AB, Lund, Sweden). In the presence of myocardial scarring, the percentage of cardiac fibrosis of the total myocardial mass was automatically estimated.

The areas of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), and thickness of right ventricular (RV) and LV EAT was determined using an ExelartAtlas 1.5 MRI scanner (Toshiba, Japan) 1 year after MI. Visceral obesity (VO) was established when the VAT area >130 cm^2 and the VAT/SAT ratio ⩾0,4.

Statistical processing was carried out using the STATISTICA 6.1 and SPSS 17.0 software. The distribution of the results was checked by the Kolmogorov-Smirnov test. The results are presented as median (Me) and quartiles (Me: Q1; Q3). Mann-Whitney U-test was used to compare the independent groups with non-normally distributed traits. Frequency differences in two independent groups were analyzed using the two-sided Fisher's exact test. An analysis of the relationship between independent variables was performed using logistic regression and ROC analysis. The differences were considered significant at $p<0,05$.

Results

The results of myocardial scarring assessment by MRI are presented in Figure 1. One year after MI, there were 68 (77%) patients with myocardial scarring and 20 patients without it. All patients were divided into 4 groups depending on presence and extent of scarring: group 1 — 20 people without cardiac fibrosis; group 2 — patients with 1-5% of scarring (n=27); group 3 — 6-15% of scarring (n=22); group 4 — >15% of scarring (n=19).

Clinical characteristics of patients depending on the extent of cardiac fibrosis are presented in Table 1. Patients of the studied groups were comparable in age, gender and risk factors for CAD, such as hypertension, obesity, diabetes, and family history of CAD ($p>0,05$). Patients with cardiac fibrosis were characterized by higher incidence of hypercholesterolemia, manifestations of angina and heart failure before the MI onset, as well as smoking history, compared with patients without scarring. The presence of previous MI and current Q-wave MI were typical for patients with scarring >5%.

Patients with cardiac fibrosis were characterized by an unfavorable prognosis during hospitalization: for example, among patients of the 2nd, 3rd and 4th groups, Killip class II acute heart failure, heart arrhythmias and early post-infarction angina were recorded.

Despite the fact that patients did not significantly differ in VAT area and VO incidence (Table 1), EAT thickness was associated with extent of cardiac fibrosis. A significant increase in EAT thickness was observed in patients with 5-15% of scarring. However, in patients with scarring >15%, the EAT thickness, on the contrary, decreased by 16% compared with patients of group 3 (6-15%) (Figure 2).

The relationship between cardiac fibrosis and EAT was confirmed by logistic regression analysis. An increase in the EAT thickness of LV and RV by 1,33 times and 1,34 times, respectively, raised the risk of cardiac fibrosis (LV EAT, mm (odds ratio (OR) 1,33; 95% confidence interval (CI) (1,08-1,4), AUC 0,75; LV EAT, mm (OR 1,34; 95% CI (1,15-1,43), AUC 0,79). It should be noted that the increase in the abdominal VAT area also raised the risk of cardiac fibrosis after MI, but the relationship was weaker than in the EAT (OR 1,21; 95% CI (1,15-1,53), AUC 0,69).

The response of cardiac tissue to injury includes a cascade of inflammatory and pro-inflammatory

Table 1

Clinical characteristics of patients with MI depending on the cardiac fibrosis, n (%)

Parameters	Group 1 Patients without cardiac fibrosis, n=20	Group 2 Patients with cardiac fibrosis <5%, n=27	Group 3 Patients with cardiac fibrosis of 5-15%, n=22	Group 4 Patients with cardiac fibrosis >15%, n=19
	n (%)	n (%)	n (%)	n (%)
Age	57,7 (51,5;63,5)	51,50 (45,0;62,0)	54,7 (52,5;64,5)	56,50 (51,0;64,2)
Gender/Male	20(100%)	18 (66,6%)	14(63,6%)	13 (68,4%)
BMI, kg/m^2	27,1(18,3:37,4)	27,4(17,1:38,1)	26,5 (19,3:33,4)	28,5 (18,3:37,1)
Obesity prevalence (BMI ⩾30,0 kg/m^2)	5 (25%)	6 (22%)	6 (27,7%)	5 (26,3%)
Smoking	19 (65,5%)	18 (66,6%)	12 (54,5%)	15 (78,9%)
Smoking	9 (45,0%)	15 (55,5%)[a]	18 (81,8%)[a,b]	17 (89,4%)[a,c]
Positive family history of CAD	1(5%)	1 (3,7%)	2 (9,1%)	2(10,5%)
History of dyslipidemia	5 (25,0%)	17 (62,9%)[a]	19 (86,3%)[a,b]	19 (100%)[a,c]
Manifestations of angina before	5 (25,0%)	12 (44,4%)	13 (59,0%)[a,b]	18 (94,7%)[a,c,d]
MI Heart failure before MI	0	3 (11,1%)[a]	10 (45,4%)[a,b]	13 (68,4%)[a,c]
History of MI	0	0	1 (4,5%)[a,b]	3 (15,7%)[a,c]
Type of acute coronary syndrome				
Q-wave MI	0	0	2 (9%)	3 (15,7%)[a,c]
Non-Q-wave MI	20 (100%)	27 (100,0%)	20 (91,0%)	16 (84,3%)
MI complications during hospitalization				
Acute heart failure (according to Killip classification) Class I	17 (85,0%)	20 (74,1%)	11 (55,0%)	8 (42,1%)
Class II	3 (15,0%)	7 (25,9%)	11 (55,0%)[a,b]	11 (57,8%)[a,c]
Newly diagnosed arrhythmia	0	8 (29,6%)[a]	12 (54,5%)[a,b]	11 (57,9%)[a,c,d]
Early post-infarction angina	2 (10%)	5 (18,5%)	8 (36,3%)[a,b]	7 (36,8%)[a,c]
Recurrent MI	0	0	0	0
Morphometric characteristics of adipose tissue by MRI				
Total area of abdominal adipose tissue, cm^2	442,8 (150,4:610,8)	483,4 (312,3:690,0)	487,0 (312,1:736,5)	511,1 (281,3:678,5)
VAT, cm^2	156,0 (64,1:258,6)	173,6 (103,3:259,3)	178,2 (64,7:355,0)	195,0 (108,3:304,4)
SAT, cm^2	286,6 (159:498)	309,8 (173,7:499,2)	308,8 (172,1:498,5)	316 ,2 (165,5:498,5)
VAT/SAT	0,54 (0,4:0,56)	0,55(0,60:0,72)	0,57 (0,37:0,71)	0,61 (0,61:0,65)

Notes: [a] — p<0,05 — the significance of differences compared with patients without cardiac fibrosis, [b] — p<0,05 — the significance of differences between groups 2 and 3, [c] — p<0,05 — the significance of differences between groups 2 and 4, [d] — p<0,05 — the significance of the differences between groups 3 and 4.

Abbreviations: VAT — visceral adipose tissue, CAD — coronary heart disease, MI — myocardial infarction, BMI — body mass index, MRI — magnetic resonance imaging, SAT — subcutaneous adipose tissue

reactions, changes in the cardiac extracellular matrix, induction and release of growth factors and cytokines. The results indicate that myocardial injury due to MI (day 1) is characterized by higher concentrations of NT-proBNP, ST2, COL-1 in patients with cardiac fibrosis (5-15% or more), compared with patients without cardiac fibrosis (Figure 3). Unlike the rest of the studied parameters, IL-33 levels significantly decreased on the 1st day of MI only in patients with cardiac fibrosis >15%. One year after MI, NT-proBNP and ST2 levels reached values of patients without cardiac fibrosis. Although the concentration of COL-1 in fibrosis patients decreased on the 12th day compared with the acute phase of MI (almost 2 times), then after 1 year in patients with fibrosis >15%,

COL-1 levels was 1,4 times higher than in the group without cardiac fibrosis.

Among the biochemical parameters, the most informative for predicting the cardiac fibrosis risk were ST2 and NT-proBNP levels both in the early period and 1 year after MI (Table 2).

In addition, correlations were found between the morphometric parameters of EAT and ST2 and NT-proBNP levels (Table 3). It was found that ST2 increase during hospitalization is positively correlated with an increase in the EAT thickness of LV and RV. The concentration of NT-proBNP, on the contrary, was inversely proportional to the EAT thickness already during hospitalization and 1 year after MI.

Thus, the development of cardiac fibrosis one year after MI is associated with an increase in ST2, NT-proBNP and COL-1 levels in the blood serum, both during hospitalization and one year after MI. A decrease in the concentration of IL-33 during hospitalization is associated with cardiac fibrosis >15%.

Discussion

Our results revealed that 77% of patients one year after MI had myocardial scarring of varying extent: <5%, from 5 to 15% and >15% of the total myocardial mass. However, there were patients without cardiac fibrosis. In order to identify predictors cardiac fibrosis, clinical, anamnestic and biochemical data collected during hospitalization and 1 year after MI were analyzed. It was established that the development of cardiac fibrosis

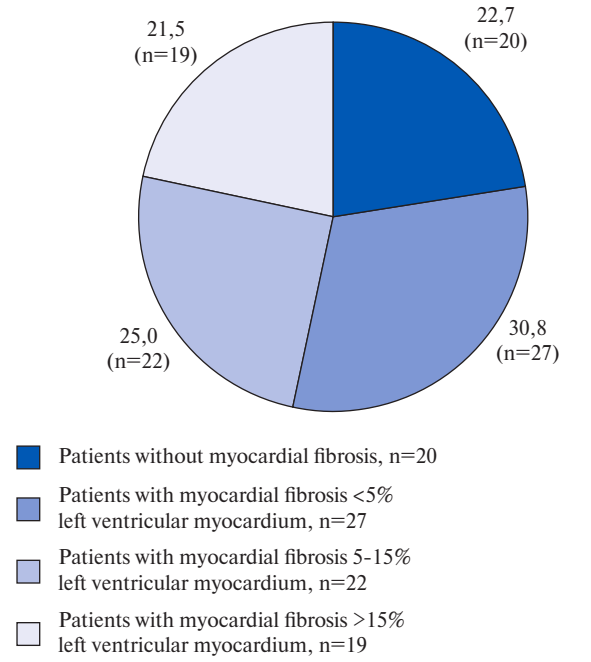

Figure 1. The extent of cardiac scarring in patients with CAD 1 year after MI.

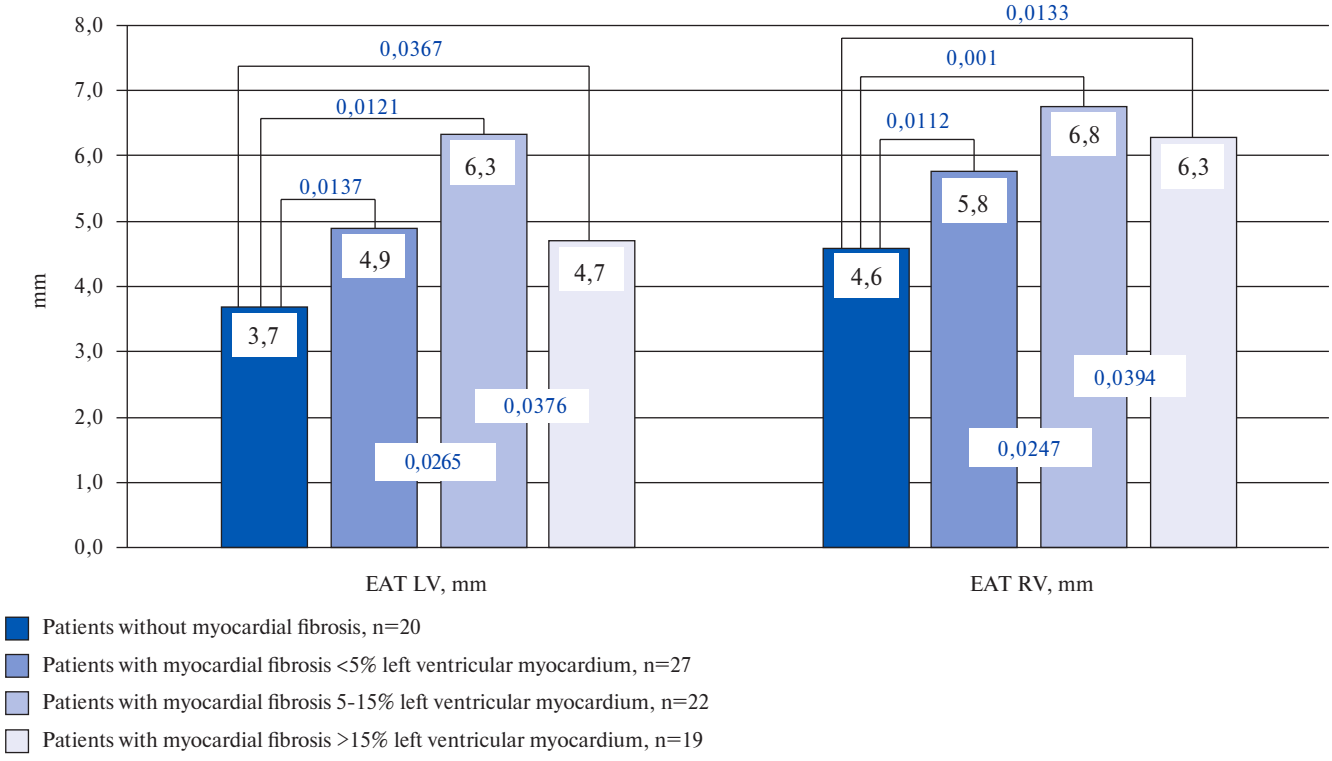

Figure 2. The EAT thickness depending on the presence of cardiac fibrosis 1 year after myocardial infarction.

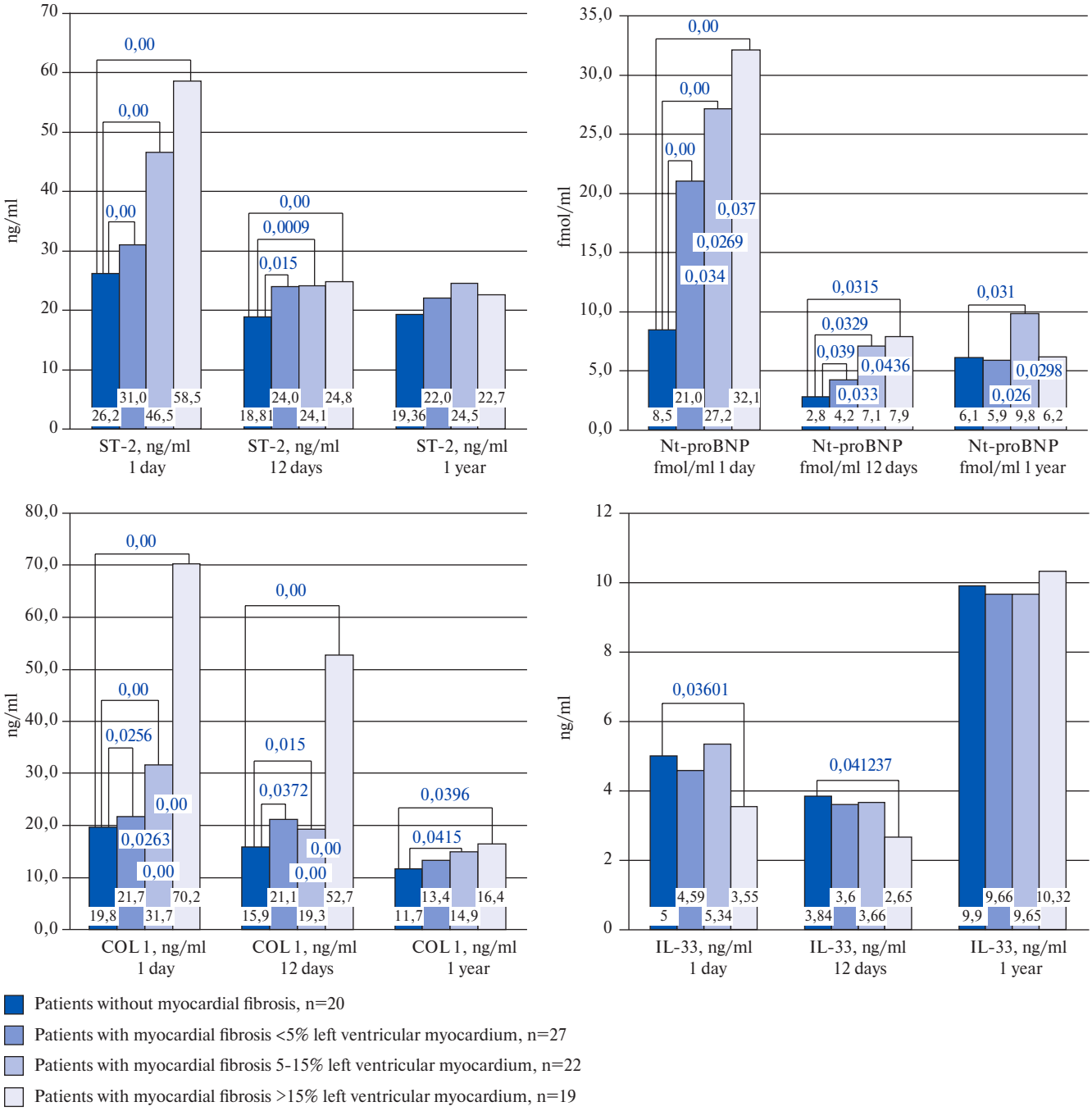

Figure 3. Biochemical parameters during and after hospitalization depending on the extent of cardiac fibrosis.

after MI is preceded by an unfavorable medical history — a high incidence of dyslipidemia, hypercholesterolemia, smoking, manifestations of angina and heart failure before MI. The presence of previous MI and current Q-wave MI was characteristic of patients with cardiac fibrosis >5% (Table 1). Probably, in this case, recurrent MI leads to more severe damage to cardiomyocytes and cardiac fibrosis.

Patients with myocardial scarring detected one year after MI had an unfavorable prognosis already during hospitalization: Killip class II acute heart failure, heart arrhythmias, and early post-infarction angina were recorded. Laboratory parameters in patients with cardiac fibrosis were characterized by an NT-proBNP increase on the 1st day; maximum value was recorded in patients with scarring >15%.

Table 2

OR, 95% CI and area under the ROC curve for cardiac fibrosis detection

Parameter	1st of MI				1 year after MI			
	OR	95% CI	p	AUC	OR	95% CI	p	OR
ST2, ng/ml	1,41	1,04-1,5	0,02	0,86	1,2	1,79-7,41	0,00	0,68
Nt-proBNP, ng/ml	1,21	0,75-2,31	0,00	0,82	1,80	0,99-4,48	0,01	0,72

Abbreviations: CI — confidence interval, MI — myocardial infarction, OR — odds ratio, AUC — area under the ROC curve, NT-proBNP — N-terminal pro-brain natriuretic peptide, ST2 — stimulating growth factor.

It is known that the 1st day of MI correspond to the acute phase, characterized by hemodynamic stress, activation of the sympathoadrenal system, inflammatory and reparative processes, as well as the fibrogenesis initiation. Hemodynamic stress in the acute phase of MI is a trigger for the expression of natriuretic peptide, which has a pleotropic effect. It increases diuresis and vasodilation, reduces the activity of the renin-angiotensin-aldosterone system, suppresses cardiac hypertrophy, myocardial fibrosis and cardiomyocyte apoptosis. In addition to the hemodynamic effects, the natriuretic peptide can cause reversible cardiac remodeling, activating antifibrotic processes and regulating key elements of fibrogenesis, such as transforming growth factor β1 and endothelin 1. In our study, NT-proBNP concentration increased, apparently due to hemodynamic stress, which reflects a more severe hemodynamic disorder in these patients.

Table 3

Spearman's correlation coefficient (r) between the levels of ST2, Nt-proBNP and the EAT thickness

Parameter	LV EAT, mm	RV EAT,mm
ST2, day 1	r=0,31; p=0,01	r=0,28; p=0,04
ST2, day 12	r=0,37; p=0,04	r=0,38; p=0,04
Nt-proBNP, day 12	r=-0,29; p=0,03	r=-0,33; p=0,01
Nt-proBNP, 1 year after	r=-0,39; p=0,03	r=-0,23; p=0,03

Abbreviations: LV EAT — thickness of left ventricular epicardial adipose tissue, RV EAT — thickness of left ventricular epicardial adipose tissue, NT-proBNP — N-terminal pro- brain natriuretic peptide, ST2 — stimulating growth factor.

It should be noted that in patients without cardiac fibrosis, there was an IL-33 increase during hospitalization (Figure 3). IL-33 binds to a ST2L and has a pro-inflammatory effect due to the inactivation of the nuclear factor-kappa B (NF-kB). The results of experimental and clinical studies have shown that IL-33 plays a regulatory role in cardiomyocyte dysfunction after MI. In an experiment, the addition of IL-33 to a cardiomyocyte culture inhibited hypoxia-induced apoptosis due to an increase in the expression of inhibitors of this process and a decrease in the activity of caspase-3 — an enzyme that enhances apoptosis [7]. Subcutaneous injection of IL-33 reduced the area of MI, fibrosis, and myocardial apoptosis. At the same time, the addition of ST2 contributed to a decrease in these effects in direct proportion to ST2 levels [3]. In addition, the IL-33/ST2 signaling pathway probably enhances the atherosclerotic plaque stability. It is well known that interferon-γ (IFN-γ) produced by T_h1 cells can stimulate the expression of matrix metalloproteinases (MMPs) by macrophages — enzymes that damage and destabilize atherosclerotic plaques. Previous studies have shown that in the acute phase of MI, the concentration of MMP-9 mainly increases in culprit coronary artery, but not in the systemic circulation. IL-33, reducing serum IFN-γ, prevents the MMP activation, destruction of the extracellular matrix and plaque rupture [8].

Probably, in patients without fibrosis, IL-33 and ST2L interaction has a cardioprotective effect and prevents and/or slows the development of cardiac fibrosis, hypertrophy and cardiomyocyte apoptosis. This cardioprotective effect is carried out exclusively through the ST2L receptor, but not through the soluble ST2 (sST2). In turn, the sST2, competing with ST2L, actively binds to IL-33 and blocks the IL-33/ST2L system. In patients with cardiac fibrosis, the cardioprotective effect of IL-33 is offset by a higher ST2 levels. According to our data, the concentration of ST2 increases by 1,2 times, 1,8 times and 2,2 times, respectively, with cardiac fibrosis <5%, 5-15% and >15%. Obviously, the greater the inhibition of cardioprotective IL-33 signaling during hospitalization, the more severe will be fibrosis after hospitalization.

It was established that not only the medical history and more severe clinical course of MI

during hospitalization are associated with myocardial scarring. So, the degree of EAT in patients after MI is interrelated with the extent of cardiac fibrosis. It is likely that an EAT increase is an unfavorable factor in the post-hospital time. The results of clinical studies demonstrate a positive relationship of the EAT volume with coronary atherosclerosis and the CVD risk [9, 10]. It is known that EAT has a phenotype closer to the EAT phenotype; in coronary atherosclerosis, it shifts towards the pro-inflammatory phenotype and, thus, contributes to the atherosclerosis progression.

An increase of the atrial EAT thickness can enhance the production of Nt-proBNP, which causes adipogenic differentiation of the multipotent mesenchymal stem cell derived from the epicardium. Epicardial mesenchymal stem cells transforms into adipocytes in response to adipogenic stimulation of cardiomyocytes. In murine models of myocardial injury, it was shown that cells derived from epicardial precursors differentiate into adipocytes around the infarct area [11]. Similarly, periatrial adipose accumulation in heart failure (HF) is considered the result of adipogenic factors secreted by dysfunctional atrial myocytes. In turn, EAT can contribute to atrial fibrosis by secreting cytokines such as activin A, or initiate atrial subepicardial fibrosis, affecting the mechanical function of the atria [12].

However, with severe cardiac sclerosis (sclerosis >15%), the EAT volume, on the contrary, decreases. The observed phenomenon of EAT "cachexia" with pronounced myocardial scarring at first glance contradicts the current opinion on the inducing atherogenic effect of EAT adipokines and cytokines on cardiomyocytes and coronary vessels. Apparently, one of the reasons for EAT cachexia in patients with severe cardiac fibrosis is the maximum expression of NT-proBNP in cardiomyocytes. It is likely that with a chronic increase of NT-proBNP concentration, its effect on lipolysis predominates over the adipogenic effect, which leads to EAT volume decrease. The conversion of the hormone effect may be associated with a change in the ratio of the A-type natriuretic peptide receptor (NPRA) to Nt-proBNP in adipose tissue and natriuretic peptide clearance receptor (NPRC), which is an important regulator of the natriuretic peptide activity of the. The binding of Nt-proBNP to NPRA causes changes in energy expenditure, metabolism, and presence of brown adipocytes in white adipose tissue [13], improving diastolic function of the heart. The Nt-proBNP NPRA receptor has a guanylyl cyclase activity. Upon binding of natriuretic peptides to NPRA in the adipocyte, the receptor guanylyl cyclase is activated, producing cyclic guanosine monophosphate (cGMP), which then activates intracellular protein kinase G (PKG) [12]. PKG phosphorylates several lipolytic proteins, including hormone-sensitive lipase, perilipin and triglyceride lipase in adipose tissue, which leads to the breakdown of accumulated triglycerides into free fatty acids (FFA). At the same time, PKG phosphorylates a mitogen-activated protein kinase (p38MAPK), which modulates the brown adipose thermogenesis, increasing the transcription of proteins such as uncoupling protein-1 (UCP-1) and gamma-coactivator 1 alpha (PGC-1α) activated by the peroxisome proliferator. UCP-1 is responsible for uncoupling of oxidative phosphorylation, and PGC1α is a key regulator of oxidative metabolism. UCP1 and PGC-1α stimulate mitochondrial biogenesis, uncoupling oxidation and phosphorylation, which leads to an increase in energy expenditure and thus limits the growth of adipose tissue. The lipolytic effect of NT-proBNP can be enhanced by a decrease in the number of NPRC that bind NT-proBNP from the circulation for internalization and degradation [14].

The activation of lipolysis in cardiac fibrosis under the Nt-proBNP action can exacerbate the clinical course during hospitalization and after discharge. It is known that FFA lipolytic products have a cardiotoxic effect. We previously showed that a high concentration of FFA in the acute phase of MI is unfavorable prognostic factor for in-hospital and long-term prognosis in this category of patients. Thus, a FFA increase significantly increased the risk of acute heart failure, post-infarction angina and heart arrhythmias in the early hospital period. A high FFA values during hospitalization was also associated with the manifestation of type 2 diabetes and one-year progression of heart failure [15].

The long-term development of cardiac fibrosis after MI was accompanied by a change in the fibrosis markers — COL-1protein, even during hospitalization, i.e., in the acute phase of MI. As it is known, myocardial fibrosis is a complex pathological process characterized by excessive proliferation of cardiac fibroblasts, abnormal deposition and distribution of collagen — the main components of the extracellular matrix. The data obtained confirm the initiation of fibrogenesis in the acute phase of MI.

The main limitation of our study may be a small number of patients.

Thus, the long-term development of cardiac fibrosis after MI is preceded by a change in the

biochemical parameters in the acute phase: ST2 and Nt-proBNP increase and IL-33 decrease. The most informative is an ST2 increase on the 1st day of MI, which increases the fibrosis risk after hospitalization by 1,4 times. High Nt-proBNP levels 1 year after MI increases the fibrosis risk by 1,8 times. EAT takes an active part in the cardiac scarring: the thickness is directly proportional to the ST2 level and inversely related to the Nt-proBNP concentration. The EAT extent increases with fibrosis of 5-15% and decreases — >15%. The use of a serum biochemistry determinants of myocardial fibrosis and cachexia of EAT together with imaging methods (MRI) can improve the diagnosis of myocardial scarring and improve stratification of CVD risk.

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Relationships and Activities: not.

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