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Assessment of the effectiveness of treatment in patients after acute coronary syndrome

Shvets D. A.[1], Povetkin S. V.[2], Karasev A. Yu.[1], Vishnevsky V. I.[3]

Aim. To assess the effectiveness of secondary drug prevention and surgical myocardial revascularization in patients with coronary artery disease (CAD) during long-term follow-up after acute coronary syndrome (ACS).

Material and methods. The study involved 400 patients with ACS discharged from the hospital in 2012-2016. The diagnosis was verified according to the European Society of Cardiology (ESC) guidelines. There were no exclusion criteria. We analyzed the data of medical records (complaints, medical history, physical examination, laboratory and instrumental data). Repeated data collection was carried out by distance survey and during a face-to-face examination during 2018. According to the clinical course of CAD, all patients were divided into 2 groups. Group 1 consisted of 151 patients with complicated course of CAD, group 2 — 249 patients with stable CAD. We analyzed drug therapy recommended at hospital discharge and taken at the time of the repeated examination. The drug names and daily dosage used for the secondary prevention of CAD were recorded. Assessment of survival without cardiovascular complications was carried out according to the Kaplan-Mayer analysis.

Results. Seven-year mortality was 22,5%. The total number of cardiovascular events was 37,7%. The main reason for the frequent complications was the insufficient secondary prevention of CAD after ACS. We found that the drugs and their dosage did not have a significant effect on survival. Statin use is associated with a paradoxical increase in the number of complications. The increased frequency of use and dosage of statins are a consequence of unfavorable course of CAD and do not have the proper preventive effect. For some groups of drugs, we observed irregular intake over the observation period. The low effectiveness of therapy is not only due to insufficient doses, but also in the frequent use of generic drugs. The significant effect of coronary angiography on the probability of cardiovascular complications compared with stenting is due to high proportion of coronary angiography use without revascularization.

Conclusion. The combination of following factors of drug therapy can explain the low effectiveness of secondary CAD prevention: low dose (26,1±2,8 mg for atorvastatin), irregular intake and common use of generic drugs (97,6% for statins). The contribution of surgical treatment to reducing cardiovascular complications is lower, the more significant residual coronary artery stenosis.

Key words: acute coronary syndrome, prevention, prediction of complications.

Relationships and Activities: not.

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The epidemic of coronary artery disease (CAD) reached the maximum in the 1960s. Over the past decades, cardiovascular mortality in all industrialized countries has been steadily declining. Primary and secondary prevention of atherosclerosis played an undeniable positive role [1-5]. Introduction of interventional treatment significantly contributed to improving the prognosis in patients with acute coronary syndrome (ACS). Nevertheless, it is believed that preventive potential has not yet been fully realized. In many patients with indications, myocardial revascularization is not performed effectively [6]. In recent decades, the researchers have created the concept of evidence-based medicine. The science-based approach allowed to reasonably introduce into clinical practice numerous therapeutic strategies and drugs that improve the prognosis of patients with CAD [4, 5]. According to studies, any prevention measures lose traction in patients with low socioeconomic status due to insufficient adherence to treatment. It is not without reason that in studies, along with conventional risk factors, authors assess the income level [7, 8]. The CAD-related standardized mortality rate in patients >50 years of age was 2153,1 for men and 1288,2 for women per 100 thousand patients with CAD. The same parameters in Russia are 2-3 times higher than in countries such as the USA, Great Britain, France, and Germany [2, 3].

The aim of secondary prevention is to reduce the incidence of cardiovascular events (CVE) by achieving the target values of lipids, blood pressure (BP) and heart rate (HR). An important component of prevention is a monitoring of patients. Especially valuable information is provided by registers with long-term follow-up [1]. In the Russian Federation, there are few registers with small number of patients and a short-term follow-up. As a result, cardiologists are forced to use the scores developed using patient registers in North America and Europe. This makes relevant the conduction of studies in Russia with long-term follow-up, assessment of the effectiveness of secondary prevention and interventional treatment of CAD.

The aim of the study was to assess the effectiveness of secondary drug prevention and surgical myocardial revascularization in patients with coronary artery disease (CAD) during long-term follow-up after acute coronary syndrome (ACS).

Material and methods

The study included 6,2% (n=400) of randomly selected patients with ACS discharged from the emergency cardiology department of the Oryol Regional Clinical Hospital in 2012-2016. All participants gave written informed consent. There were no exclusion criteria. We analyzed the data of medical records (complaints, medical history, physical examination, laboratory and instrumental data). Repeated data collection was carried out by distance survey (by telephone or mail), by request to Civil Registry Department of the Oryol Region (death cases), and by face-to-face examination (rehospitalization or outpatient visit). A telephone survey of patients and relatives was carried out during 2018 and included patients rehospitilized until 2018. Thus, 211 patients (52,7%) were re-examined in face-to-face manner, 152 patients — by distance survey (by telephone or mail), and 37 deaths were registered by request to Civil Registry Department.

Upon re-examination of patients, the levels of blood pressure (BP), heart rate (HR), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were determined. The delta% of all parameters was calculated using the formula — ((end value-initial value)/initial value)*100%. Hyperlipidemia was established at TC >5 mmol/L and LDL-C >2,5 mmol/L.

All patients were divided into 2 groups depending on the clinical course of CAD. The criterion for separation into groups was the registration of one of the following major adverse cardiac events (MACE): cardiovascular death, recurrent ACS (unstable angina, myocardial infarction (MI)), stroke, repeat myocardial revascularization, ischemic cardiomyopathy (ICMP) with progressive heart failure (HF) [5, 9]. Group 1 consisted of 151 patients with a complicated course of CAD, group 2 — 249 patients with a stable course of CAD (Figure 1).

Figure 1 shows that most frequent MACE were cardiovascular death and repeated ACS (95,1%). Death was considered cardiovascular by reliable clinical, instrumental and autopsy data, including cases where other causes were unlikely. The 7-year mortality was 22,5%.

Table 1 presents the clinical characteristics of patients.

We analyzed therapy, recommended at discharge and received at the time of re-examination/questioning. The name and daily dosage of drugs from the main pharmacological classes used for the secondary prevention of CAD were taken into account: statins, beta-1 blockers (BB), angiotensin converting enzyme inhibitors (ACE inhibitors)/angiotensin II receptor blockers (ARB), and antiplatelet agents. We also analyzed the effects of different drug dosages on the probability of MACE. For statins, low and moderate doses were considered 10-20 mg/day, and optimal — 30-40 mg/day (equivalent to atorvastatin). For BB, the lowest dose was 2,5 mg/day, and optimal — 5-10 mg/day (equivalent to bisoprolol). For ACE inhibitors/ARB, the low dose was up to 10 mg/day and 50 mg/day, and optimal — 20 mg/

day and 100 mg/day (equivalent to enalapril and losartan, respectively) [10].

For statistical processing, parametric and non-parametric statistics were used. In normally distributed traits (estimated by the Kolmogorov-Smirnov test), the Student's t-test was used to determine the significance of the differences. In non-normally distributed traits, a comparison was made by the Mann-Whitney U-test. Yates's chi-squared test was used for frequency comparison. The data in the tables are presented as mean (M) and standard deviation (SD) for the parametric tests and as the median [Q1; Q3] for the nonparametric tests. Evaluation of the treatment effects on the survival of patients without MACE was carried out by constructing Kaplan-Meier survival curves Differences in empirical survival functions were evaluated by Gehan-Wilcoxon test. The differences were considered statistically significant at $p<0,05$.

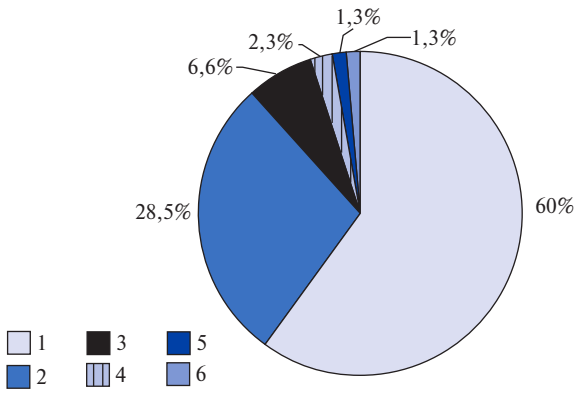

Figure 1. The proportion of major adverse cardiovascular events. **Note:** 1 — deaths (60%); 2 — unstable angina (28,5%); 3 — myocardial infarction (6,6%); 4 — repeated myocardial revascularization (2,3%); 5 — acute cerebrovascular accident (1,3%); 6 — ischemic cardiomyopathy with progressive heart failure (1,3%).

Results

Table 1 shows that patients with a complicated clinical course of CAD are initially older, more likely to have hypertension, have a more severe heart failure (according to NYHA classification) and higher mortality risk estimated by GRACE2

Table 1

Clinical characteristics of patients with coronary artery disease included in the study (M±SD), (n, %)

Parameter			Complicated clinical course (n=151)	Stable clinical course (n=249)	p
Mean age, years			64,2±12,0	59,4±11,3	<0,001
Gender	Men		96 (63,6)	173 (69,5)	>0,05
	Women		55 (36,4)	76 (30,5)	>0,05
Risk factors of coronary artery disease	Hypertension		132 (87,4%)	196 (78,7%)	<0,05
	Smoking		51 (33,8)	115 (46,2)	<0,05
	Dyslipidemia		76 (50,3)	129 (51,8)	>0,05
	Diabetes		30 (19,8)	39 (15,7)	>0,05
	Body mass index, kg/m^2		28,4±5,4	28,6±4,8	>0,05
Disease	MI	Anterior	55 (36,4)	73 (29,3)	>0,05
		Inferior	33 (21,8)	83 (33,3)	<0,01
	Unstable angina		63 (41,8)	93 (37,4)	>0,05
Heart failure (NYHA)		Class 1	20 (13,2)	59 (86,8)	<0,001
		Class 2	67 (44,4)	147 (55,6)	<0,05
		Class 3	64 (42,4)	43 (57,6)	<0,01
Mortality risk (GRACE2 and TIMI)	Low		97 (64,2)	215 (86,3)	<0,001
	Moderate		44 (29,1)	30 (12,0)	<0,001
	High		10 (6,7)	4 (1,7)	<0,01
Number of CA			69 (45,7)	164 (65,9)	<0,001
Number of PCI			46 (30,5)	105 (42,2)	<0,05
Drug therapy before hospitalization	Statins		28 (18,5)	24 (9,6)	<0,05
	BB		41 (27,1)	63 (25,3)	>0,05
	ACE inhibitors/ARB		60 (39,7)	84 (33,7)	>0,05
	Antiplatelet agents		52 (34,4)	63 (25,3)	<0,05

Abbreviations: MI — myocardial infarction, PCI — percutaneous coronary intervention, CA — coronary angiography, BB — beta-1 blockers, ACE inhibitors — angiotensin-converting enzyme inhibitors, ARB — angiotensin II receptor blockers.

and TIMI scores. The proportion of smokers was less, possibly due to the larger number of women in the group with complicated course of CAD. Patients of group 1 received statins and antiplatelet agents more often before entering the study. This possibly due to more severe patients' condition: less cases of inferior MI, and more — anterior MI and unstable angina.

Figure 2 shows that lipid normalization leads to improving the survival without MACE.

There were following TC values: group 1 — 5,4 [4,3; 6,8] mmol/L; group 2 — 4,5 [3,7; 5,3] mmol/L; $p<0,05$.

Figure 3 shows that patients with stable clinical course of CAD had a LDL-C decrease by more than 20%.

Thus, despite a significant decrease, LDL-C values did not reach the target level (<1,8 mmol/L according to ECC guidelines).

At the same time, statin administration did not have a prognostic value in reducing the number of MACE (Figure 4).

Moreover, statin therapy was associated with lower survival. It turns out that statin use and lipid profile changes affect prognosis in different ways. Consequently, lipid profile changes and prognosis improvement are difficult to associate with the statin use.

An analysis of the survival without MACE depending on the statin dosages was made (Figure 5).

An increased dose of statins confirms the above findings about the negative effects of statins on survival.

Figure 6 shows the Kaplan-Mayer curve, which demonstrates the association between BB administration and incidence of MACE.

It can be seen that patients taking BB did not have reduced MACE risk.

Figure 7 shows the dependence of delta% HR on the actual BB intake upon re-examination.

It can be seen that BB administration slightly affects HR, and without BB, it increases by 8%. Statistical analysis showed that delta% HR does not affect the probability of MACE.

There were no differences in MACE incidence depending on BB dosage (Figure 8).

The effects of ACE inhibitors/ARB on the MACE incidence were studied (Figure 9).

There were no statistically significant effects of ACE inhibitors/ARB on the survival of patients without risk of MACE.

Figure 10 shows the dependence of delta% SBP on the clinical course of CAD.

A significant difference of delta% SBP was revealed. In a stable course of CAD, a decrease in SBP was by 3,7% [-15,4; 7,7]. The same differences regarding DBP were not revealed.

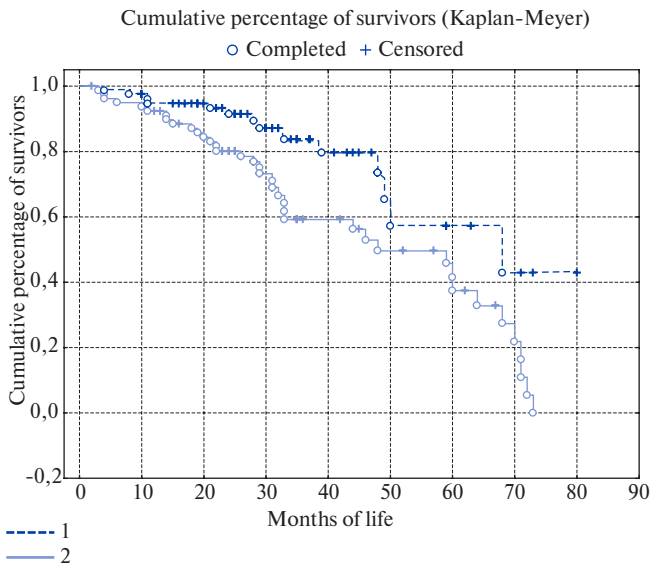

Figure 2. The Kaplan-Mayer curves for the patients without MACE with different changes of the lipid profile.
Note: 1 — lipid profile normalization; 2 — preserved hyperlipidemia; $p<0,05$. At the re-examination time, in the group of complicated clinical course of CAD (n=53), there were 19 patients with hyperlipidemia (64,1%); in the group of stable clinical course of CAD (n=105), there were 35 patients with hyperlipidemia (33,3%). $\chi^2 = 13,6$; p=0,0004.

Figure 11 shows the survival curves in patients without MACE depending on the intake of low or increased doses of ACE inhibitors/ARB. There was no statistically significant difference. However, there was a tendency towards MACE decrease with high doses of ACE inhibitors/ARB.

Figure 12 shows the survival curves depending on the intake of antiplatelet agents. Administration of antiplatelet agents did not significantly decrease the incidence of MACE.

We compared the treatment with four-component therapy (statins, BB, ACE inhibitors/ARB, and antiplatelet agents) and without taking any medication with respect to the risk of MACE. Upon re-examination, no statistically significant differences were found.

To find the reasons for the low effectiveness of drug therapy in the secondary prevention, we analyzed the frequency of use of the branded and generic medicines in patients after ACS (Figure 13).

Most often, patients used branded BB (Concor®, Betaloc® ZOK, Nebilet®). Therefore, this class can be used as an example to consider the effect of branded and generic medicines on survival without MACE (Figure 14).

There was no significant difference in the effect on the prognosis; however, taking the branded medicines at the optimal dose is characterized by a tendency towards better survival of patients without

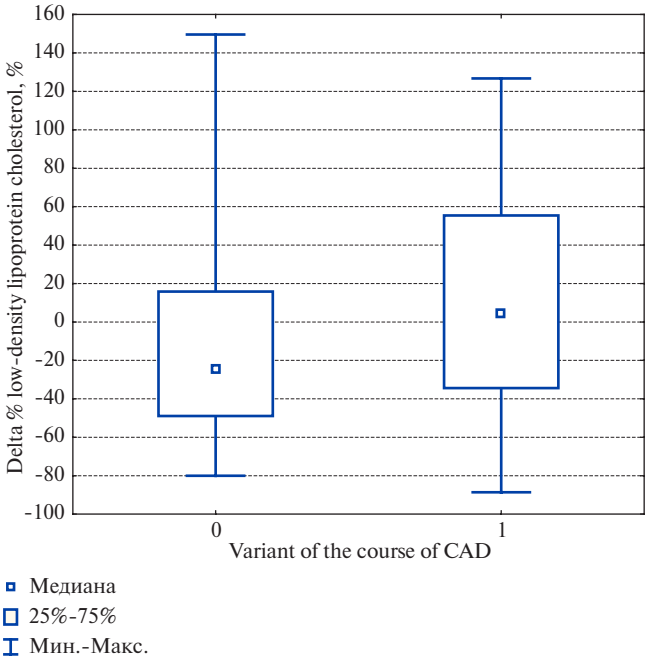

Figure 3. Comparison of delta% of LDL-C depending on the CAD course.
Note: 0 — stable clinical course of CAD; 1 — complicated clinical course of CAD; p<0,05. The median of LDL-C at re-examination time: group of stable clinical course of CAD — 2,78 [2,0; 3,45]; group of complicated clinical course of CAD — 3,6 [2,6; 4,7].

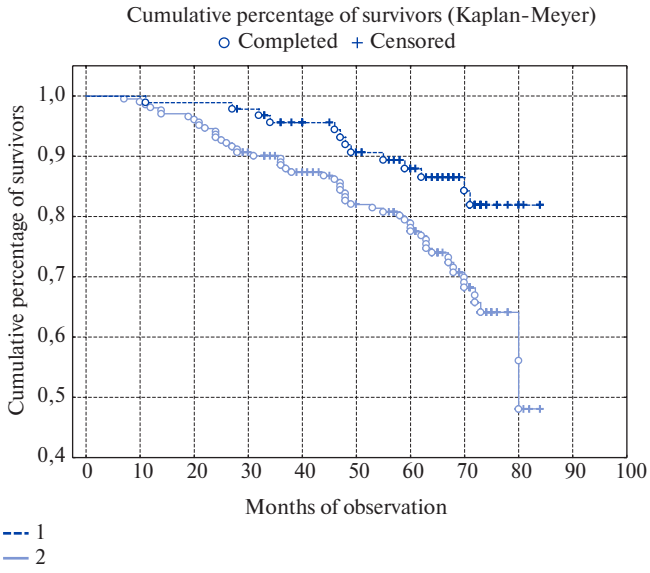

Figure 4. Kaplan-Mayer curves for the patients without MACE and with/without statin therapy.
Note: 1 — without statins; 2 — with statins; p<0,01. In the group of complicated clinical course of CAD (n=72), 59 patients took statins (81,9%). In the group of stable clinical course of CAD (n=225), 146 patients (64,9%) took statins. χ^2=7,4; p=0,01.

MACE [11]. At the same time, we recorded the wave-like nature of the curve divergence: the initial curve divergence after 1 year of treatment was followed by merging until the end of 4 years of follow-up. Such

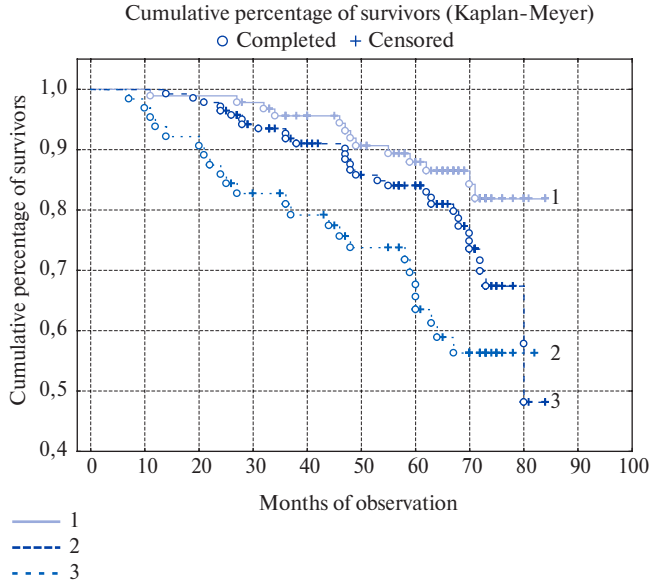

Figure 5. Kaplan-Mayer curves for patients without MACE depending on the statin dose.
Note: 1 — without statins; 2 — low-dose statins; 3 — dose of statins recommended by ECC*; * — p<0,001 (compared with patients not taking statins).
In the group of complicated clinical course of CAD, 13 patients (18,0%) did not take statins, 37 — low-dose statins (51,4%), and 22 — recommended statin dose (30,6%). In the group of stable clinical course of CAD, 79 patients (35,1%) did not take statins, 111 — low dose statins (49,3%), and 35 — recommended statin dose (15,6%). Differences were revealed among patients not taking statins (p=0.009) and patients taking the recommended dose of statins (p=0,006).

changes are possible with irregular treatment, when periods of optimal treatment are followed by low-dose therapy or complete drug withdrawal.

Figure 15 shows the peak number of MACE (except for deaths) during the entire follow-up.

At the beginning of the second year, the effectiveness of secondary prevention is reduced, which leads to an increase in the number of MACE. The peak number of MACE (except for deaths) was observed in the fourth year of follow-up. It is possible that with an increase in the MACE (except for deaths) number, drug therapy intensifies. This, perhaps, contributes to an increase in the effectiveness of prevention with drugs, leading to a divergence of survival curves (Figure 14).

According to the ECC guidelines, mortality risk (GRACE2 and TIMI) was estimated for all patients with ACS, on the basis of which the indications for interventional management were determined. Overall, coronary angiography (CA) were performed in 57,2% (n=229) of all patients with ACS. According to the results, 204 patients with significant coronary stenosis were identified, and 74,0% (n=151) of them underwent percutaneous coronary intervention (PCI). The remaining 26% (n=53) of patients had

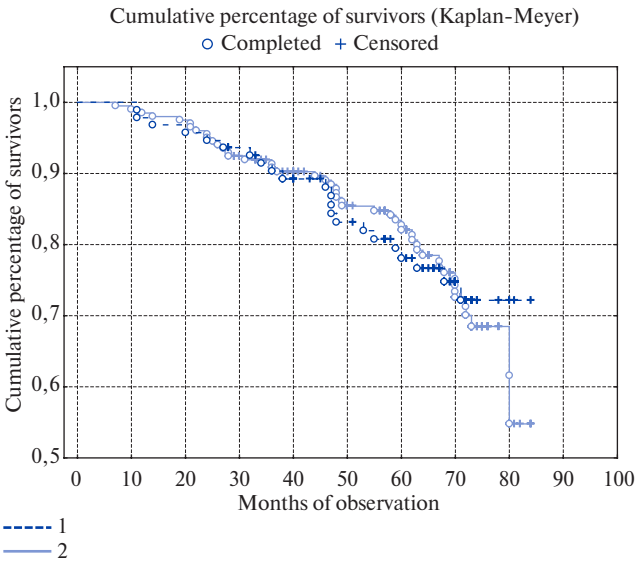

Figure 6. Kaplan-Mayer curves for patients without MACE and with/without BB therapy; p>0,05**.**
Note: 1 — without BB; 2 — with BB.
In the group of complicated clinical course of CAD (n=72), 50 patients took BB (69,4%). In the group of stable clinical course of CAD (n=224), 152 patients (67,8%) took BB. χ^2=0,06; p>0,05.

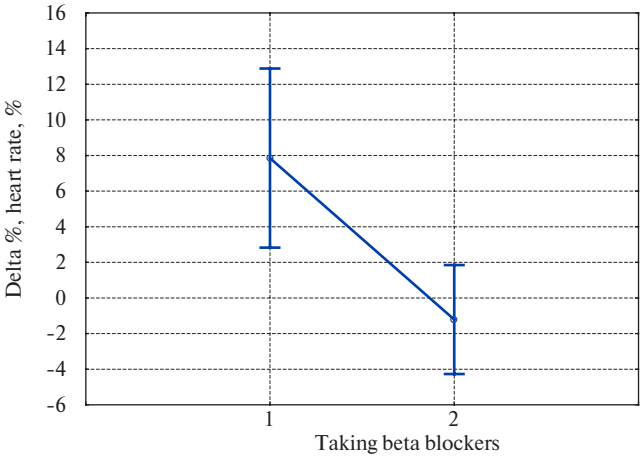

Figure 7. Dependence of delta% of heart rate and BB administration.
Note: 1 — without BB; 2 — with BB; p<0,01.

significant single, double, and triple vessel disease, and due to technical difficulties revascularization was not performed. In such cases, at discharge, we recommended revascularization in the federal center. Twenty five patients had insignificant coronary stenosis or its absence (n=2). In these cases, revascularization was not indicated.

Figure 16 shows the survival curves of patients without MACE depending on the surgical strategies.

It can be seen that there was a tendency towards a decrease in the number of MACE after PCI.

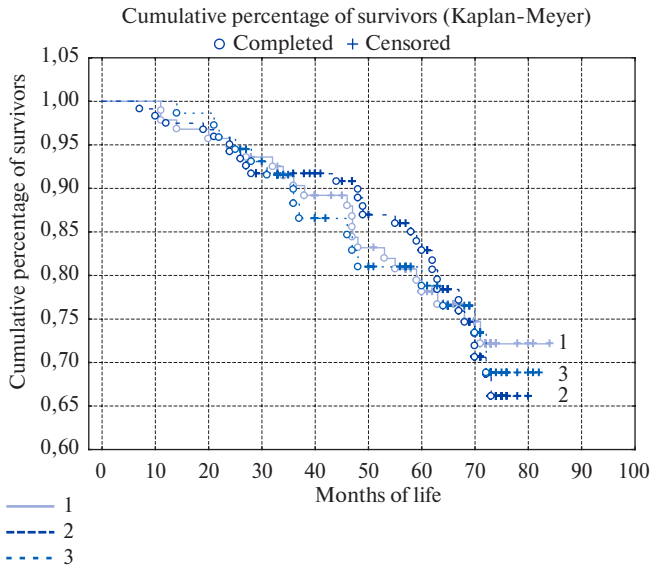

Figure 8. Kaplan-Mayer curves for patients without MACE depending on the BB dose.
Note: 1 — without BB; 2 — low-dose BB; 3 — moderate- and high-dose BB; p>0,05.
In the group of complicated clinical course of CAD, 22 patients did not take BB (30,5%), 33 — low-dose BB (45,8%), and 17 — moderate- and high-dose BB (23,7%). In the group of stable clinical course of CAD, 72 patients (32,1%) did not take BB, 95 — low-dose BB (42,4%), and 57 — moderate- and high-dose BB (25,5%). No differences were found (p>0,05).

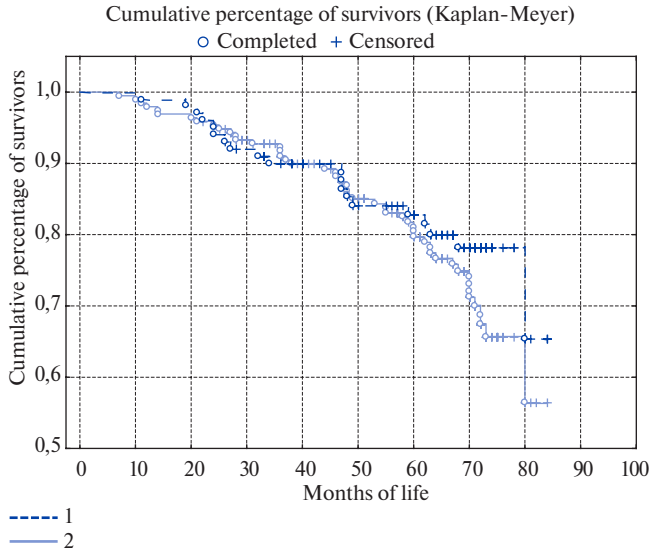

Figure 9. Kaplan-Mayer curves for patients without MACE and with/without ACE inhibitors/ARB therapy.
Note: 1 — without ACE inhibitors/ARB; 2 — with ACE inhibitors/ARB; p>0,05.
In the group of complicated clinical course of CAD (n=71), 51 patients took ACE inhibitors/ARB (71,8%). In the group of stable clinical course of CAD (n=225), 145 patients (64,4%) took ACE inhibitors/ARB. χ^2=1,3; p>0,05.

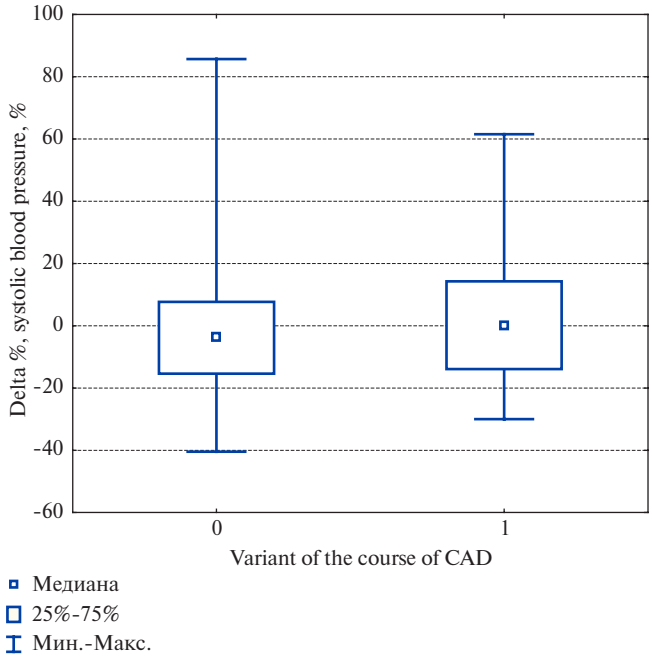

Figure 10. Dependence of delta% of SBP and patients receiving ACE inhibitors/ARB.
Note: 1 — without ACE inhibitors/ARB; 2 — with ACE inhibitors/ARB; p<0,05.

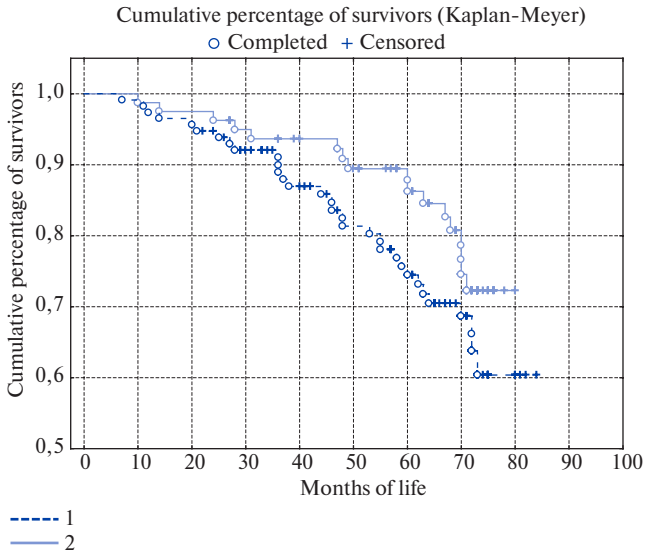

Figure 11. Kaplan-Mayer curves for patients without MACE depending on ACE inhibitors/ARB dose.
Note: 1 — low-dose ACE inhibitors/ARB; 2 — optimal dose of ACE inhibitors/ARB; p>0,05.
In the group of complicated clinical course of CAD, 32 patients (62,7%) took a low-dose ACE inhibitors/ARB, 19 — optimal dose of ACE inhibitors/ARB (37,3%). In the group of stable clinical course of CAD, 78 patients (53,8%) took a low-dose ACE inhibitors/ARB, 67 patients (46,2%) — optimal dose of ACE inhibitors/ARB. No differences were found (p>0,05).

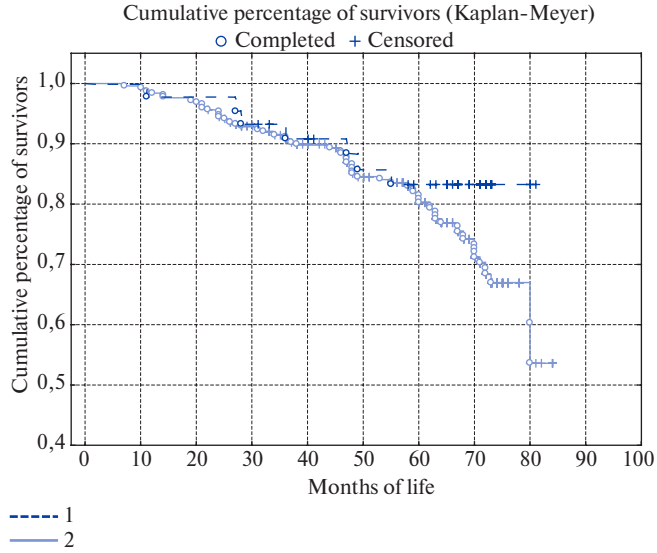

Figure 12. Kaplan-Mayer curves for patients without MACE and with/without taking antiplatelet agents.
Note: 1 — without antiplatelet agents; 2 — with antiplatelet agents; p>0,05.
In the group of complicated clinical course of CAD (n=71), 64 patients took antiplatelet agents (90,1%). In the group of stable clinical course of CAD (n=253), 189 patients (74,7%) took antiplatelet agents. χ^2=1,6; p>0,05.

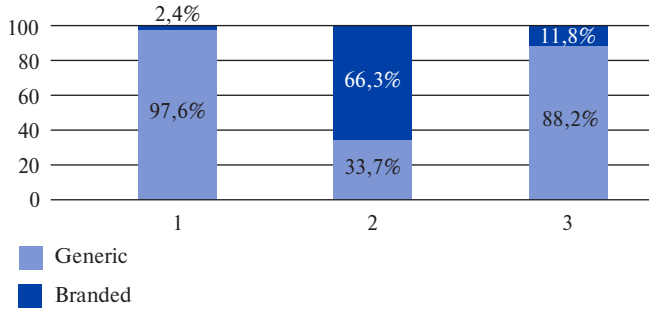

Figure 13. The percentage of the branded and generic medicines of the main drug groups used for secondary prevention in studied patients after ACS.
Note: 1 — statins (n=205); 2 — BB (n=202); 3 — ACE inhibitors/ARB (n=196).

Performing of CA significantly affected the MACE risk (Figure 17).

As can be seen, survival in patients without MACE significantly increased if CA was performed.

Discussion

The study involved 78% of patients with low risk of ACS. Despite this, the mortality rate for 7 years was 22,5%. The total number of cardiovascular events was 37,7%. In comparison, according to the GRACE register, 5-year mortality in patients with initially higher risk of ACS was 20% [1]. The reason for such findings in our study may be associated with improper

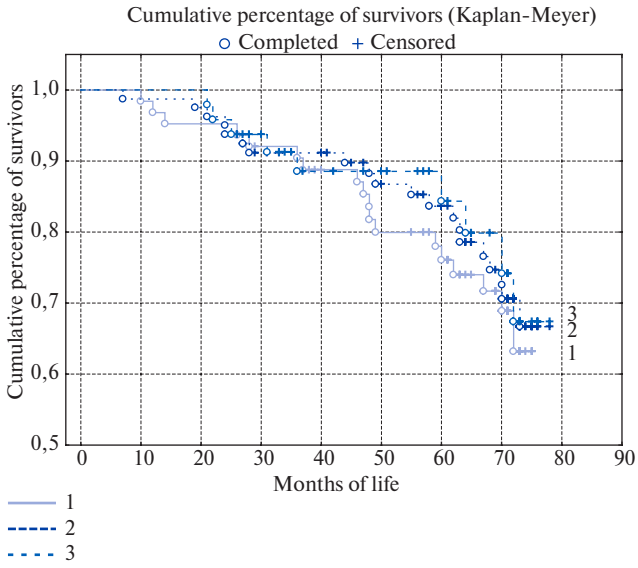

Figure 14. Kaplan-Mayer curves for patients taking various BB and survived for a certain period without MACE**.**
Note: 1 — generic BB; 2 — low-dose branded BB; 3 — branded BB in the optimal dose; p>0,05.
In the group of complicated clinical course of CAD, 19 patients took generic BB (38%), 21 — low-dose branded BB (42%), 10 — branded BB in the optimal dose (20%). In the group of stable clinical course of CAD, 48 patients took generic BB (31,5%), 66 — low-dose branded BB (43,5%), 38 — branded BB in the optimal dose (25%); p>0,05.

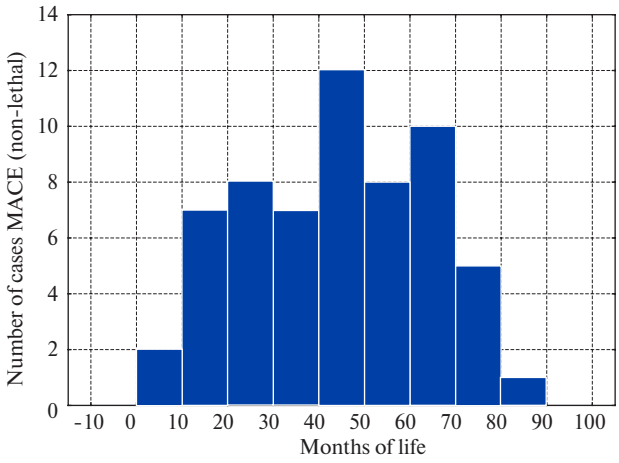

Figure 15. The distribution of MACE (except for deaths) during follow-up in patients with CAD. The median time of MACE is 47 [27,5; 62,5] months.

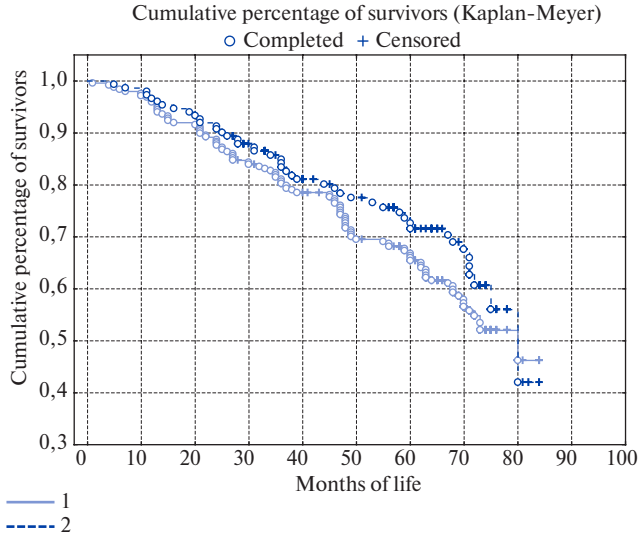

Figure 16. Kaplan-Mayer curves for patients without MACE depending on surgical strategy.
Note: 1 — without PCI; 2 — with PCI; p>0,05. In the group of complicated clinical course of CAD, there were 46 cases of PCI (30,5%). In the group of stable clinical course of CAD, there were 105 cases of PCI (42,2%). χ^2=5,5; p<0,05.

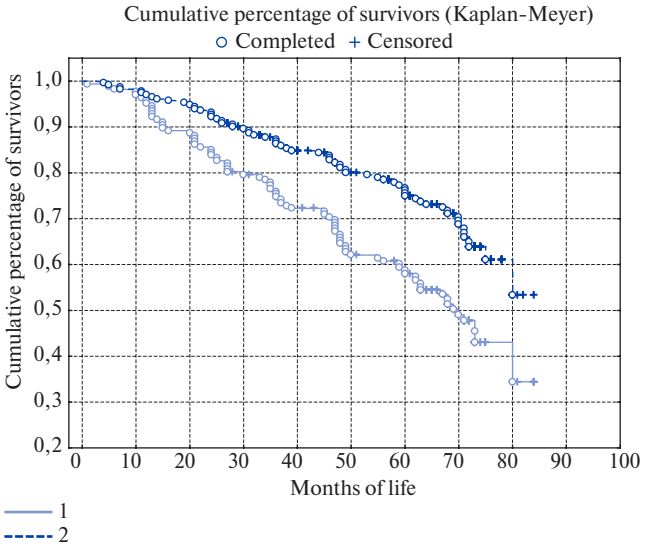

Figure 17. Kaplan-Mayer curves for patients without MACE depending on the CA.
Note: 1 — without CA; 2 — with CA; p<0,001. In the group of complicated clinical course of CAD, there were 69 cases of CA (45,7%). In the group of stable clinical course of CAD, there were 164 cases of CA (65,9%). χ^2=15,7; p<0,0001.

secondary prevention after ACS. On the one hand, we see that the effects of the main drug classes are consistent with generally accepted concepts. Delta% of blood lipids, HR and SBP in the group of patients without MACE show positive changes. On the other hand, long-term follow-up did not revealed significant effect of taking the main classes of drugs and their dosages on the survival of patients without MACE after ACS. Statin use was associated with paradoxical negative effect on the prognosis. This can be explained by the non-optimal use of medications. In addition to the ignorance of the clinical

guidelines, a significant role is played by misinterpretation of the "non nocere" principle, when doctors prescribe the lowest doses of drugs. Instead of therapy, we obtain the illusion of treatment, because prescribing a drug from the recommended group without proper dosage does not guarantee the effectiveness of the treatment.

A paradoxical response to medicines was revealed only with statins. This is due to prevailing opinion about the statin toxicity. During hospitalization and upon discharge, all patients are prescribed full-dose treatment and prevention with statins (atorvastatin 40 mg or rosuvastatin 10-20 mg). Some asymptomatic patients, mostly young, discontinue the treatment for no reason. In majority of patients, primary care physicians reduce statin's dose by half based on TC monitoring. It is noted that the initial atorvastatin dosage of 40 mg after 1-2 years is reduced to <20 mg. At the same time, only the TC levels are controlled. Some patients discontinue statin therapy due to adverse effects: heaviness in the right hypochondriac region, bitter taste in the mouth, muscle weakness and myalgia. Laboratory tests justifying drug withdrawal, as a rule, is not carried out. Thus, 1-2 years after ACS, the number of patients taking statins and its dosage are reduced. By this time period, clopidogrel is discontinued (according to the ECC guidelines). Therefore, by 2-4 years of observation, the number of MACE increases. In patients with recurrent episodes of ACS, statin therapy is resumed at previous doses. At the re-examination, statins were taken by 69% of patients; the average dose (equivalent to atorvastatin) was 26,1±2,8 mg. Consequently, the increased frequency of use and dosage of statins are a consequence of the complicated clinical course of CAD and do not have the proper preventive effect. Arguably, the intensity of therapy is specified by the disease severity.

Evidence of irregular drug intake during the follow-up period may be a divergence of the survival curves in patients without MACE 4 years after the ACS. This period corresponds to the peak number of MACE (except for deaths), which leads to intensification of drug therapy and positive survival changes. This relationship was found for BB and ACE inhibitors/ARB.

The low effectiveness of therapy is not only due to low doses. Comparison between use of recommended doses and low-dose therapy or complete drug withdrawal did not revealed significant differences in survival of patients without MACE. In our opinion, this is due to the low effectiveness of the drugs. Generic medicines may not have the same complete effect as the branded ones. Observed paradoxical effect of statins can be explained not only by low doses, but also by the high prevalence of generic medicines. The problem of cheap and probably low-effective generic medicines lies not only in the pharmacology, but also in the socio-economic aspects, and therefore it cannot be solved only by developing new guidelines. It is necessary to create a register of all generic medicines with description of their coefficient of equivalence to the branded ones.

The low prognostic significance of PCI and the significant effect of CA in reducing the MACE risk are due to high percentage of patients (26%) who had single, double, and triple vessel disease revealed by CA, and PCI was not performed due to technical difficulties. In this case, discharge recommendations included revascularization in the federal center. It is likely that cases of revascularization in the federal center (PCI or CABG), together with optimization of secondary drug prevention, significantly deviate the survival curve after CA (especially by the 4th year of follow-up). Therefore, given all cases of delayed revascularization, it can be said that PCI can significantly affect survival without MACE. It can be expected that the most significant preventive effect is to reduce the mortality risk. CA cases without significant coronary stenosis can also affect the survival of patients without MACE, reducing the number of cases with incorrectly diagnosed unstable angina. Rehospitalization of a patient with provisional diagnosis of ACS, who had a history of CA without significant coronary stenosis, makes a doctor search for other causes of chest pain. Thus, the diagnosis of unstable angina may be confuted. Therefore, previously performed CA reduces the number of incorrect diagnoses of ACS.

Conclusion

The combination of following factors of drug therapy can explain the low effectiveness of secondary CAD prevention: low dose (26,1±2,8 mg for atorvastatin), irregular intake and common use of generic drugs (97,6% for statins). The contribution of surgical treatment to reducing cardiovascular events is lower, the more significant residual coronary artery stenosis.

Relationships and Activities: not.

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Novel score for mortality risk prediction 6 months after acute coronary syndrome

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Aim. To create a prediction score for assessing the mortality risk 6 months after hospitalization with acute coronary syndrome (ACS).

Material and methods. Based on the results of ACS RECORD-3 register (Russia), we determined independent mortality predictors 6 months after ACS by performing multivariate regression analysis in patients discharged alive from the hospital with known outcomes.

Results. The following predictors were obtained during the analysis: non-prescription of aspirin at discharge (odds ratio (OR) 5,8; 95% confidence interval (CI) 2,3-15,0; p<0,0001), newly diagnosed heart failure, pulmonary edema or shock in a hospital (OR 5,7; 95% CI 2,6-12,7; p<0,0001), age ⩾75 years (OR 5,3; 95% CI 2,7-10,6; p<0,0001), non-prescription of beta-blockers at discharge (OR 5,0; 95% CI 2,3-10,8; p<0,0001), in-hospital management without immediate percutaneous coronary intervention (PCI) (primary PCI during ST-segment elevation ACS or PCI during the first 72 hours in non-ST-segment elevation ACS) (OR 3,9; 95% CI 1,6-9,8; p=0,004), the initial serum creatinine ⩾100 μmol/L (OR 3,1; 95% CI 1,6-6,1; p=0,001), body mass index <30 kg/m^2 (OR 2,8; 1,2-6,3; p=0,014). Each of them was evaluated at one point and was a component of the RECORD-6 score. Prediction sensitivity and specificity for the new score were 73,3% (95% CI 60,1-83,5) and 71,4% (95% CI 68,9-73,7), respectively; prediction accuracy, estimated as the area under the ROC curve was 0,931 (95% CI 0,897-0,964). The cut-off point was considered 3 points, which had the best ratio of prediction sensitivity and specificity. The mortality after 6 months with a value of <3 points was 1,6%, and with a value of ⩾3 points — 10,1% (relative risk (RR) 0,16; 95% CI 0,09-0,28; p<0,0001), and the mortality after 12 months was 7,8% and 22,5%, respectively (RR 0,35; 95% CI 0,25-0,49; p<0,0001). Relative to the GRACE risk score for 6-month mortality, the prediction value of the RECORD-6 score was at least no worse.

Conclusion. The novel RECORD-6 risk score is an accurate and simple prediction tool for assessing the mortality risk 6 months after discharge from the hospital. The prediction accuracy of the RECORD-6 risk score is not lower the GRACE risk score.

Key words: acute coronary syndrome, prediction score, 6 months, RECORD, GRACE, long-term outcomes, death.

Relationships and Activities: not.

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Determining the prognosis in patients with acute coronary syndrome (ACS) is an important and inherent element of the entire treatment process. Given the many factors affecting the prognosis and their "weight", in practice, the prognosis often requires the use of special prognostic scales, combining several significant predictive factors. In ACS, for example, the GRACE and the TIMI are the most commonly used risk scores. Current clinical guidelines suggest the use of PRECISE-DAPT and DAPT scores to determine the risk of bleeding and the duration of dual antiplatelet therapy [1].

At present, prognostic scores are rarely used to assess the long-term risk of adverse events. Although the current version of the GRACE risk score is highly sensitive and specific for predicting the 6-month mortality risk after ACS [2], it is also little used in practice. At the same time, the importance of assessing long-term risk, especially after discharge from the hospital after ACS, is obvious, since this data can be potentially useful for subsequent outpatient management.

The aim of this analysis was to create a prediction score for 6-month mortality after hospitalization with ACS.

Material and methods

The analysis was performed based on the data of ACS RECORD-3 register (Russia) — a short-term prospective observational study, which included all hospitalized patients for 1 month (March-April 2015, 47 hospitals of 37 Russian cities; n=2370). Detailed information on the features and the main results of the RECORD-3 register was presented in previous publications [3].

Follow-up 6 months after ACS onset was carried out in 34 participating hospitals (n=2009) by telephone surveys. Data on 454 patients were not received. Data on 113 patients who died during hospitalization were excluded. Thus, the present analysis was performed on 1433 survivors after hospitalization, about which there were data on adverse events 6 months after the ACS onset.

The parameters of the novel risk score were independent predictors of 6-month mortality after the ACS onset and hospitalization.

Statistical processing was performed using software packages Statistica 10.0 and IBM SPSS Statistics 22. Discrete variables were compared using Yates's chi-squared test. To identify factors associated with 6-month post-ACS mortality, a step-by-step multivariate logistic regression analysis was performed. The studied factors were included in multivariate regression analysis if they were associated with the outcome with a significance level of $p<0,1$. The estimation of the relative risk was performed using the online calculator on the website www.medstatistic.ru. Comparison of the prognostic value of the risk scores was carried out by comparing the areas under ROC curves and using the McNeil test (www.vassarststs.net/roc_comp.html).

Results

Results of multivariate regression analysis. According to a univariate regression analysis, more than 50 anamnestic, laboratory, and clinical factors, as well as factors related to the characteristics of treatment and outcomes during hospitalization, were associated with the 6-month post-ACS mortality and were included in multivariate regression analysis. Independent predictors of 6-month mortality, identified by multivariate analysis, are presented in Table 1.

Creation of a prognostic score. The creation of the prognostic score was carried out in two fairly similar ways. According to one of them, each factor identified in multivariate regression analysis was assigned a value equal to its average odds ratio value. Thus, there was a score with a minimum value of 0 and a maximum value of 32 points ("advanced version score"). In another way, each factor was assigned 1 point, and there was a minimum value of 0 and a maximum value of 7 points ("simplified version score"). The prognostic value of these scores was compared using the ROC curve. The area under the ROC curve for the "advanced version score" was 0,935 (95% confidence interval (CI) 0,900-0,970), and for the "simplified version score" — 0,931 (95% CI 0,897-0,964) (Figure 1). The statistical difference of these values was not significant. For the "advanced version score", the prognostic sensitivity was 78,3% (95% CI 65,5-87,5), and specificity — 57,6% (95% CI 54,9-60,2). For the "simplified version score", the prognostic sensitivity was 73,3% (95% CI 60,1-83,5), and specificity — 71,4% (95% CI 68,9-73,7).

Thus, given the absence of significant difference in the area under the ROC curves of two presented versions, the similar sensitivity and specificity values, and undoubted simplicity in the calculations of "simplified version score", we chose it as a novel prognostic score, where each factor is assigned 1 point (Table 2).

Assessment of the RECORD-6 score prognostic value. The proportion of non-surviving patients depending on the RECORD-6 score data is presented in Figure 2. It can be seen that with increasing scores, the mortality rate progressively raised.

The cut-off point for the RECORD-6 score determining the low and high mortality risk after 6 months was value of 3 points. According to the ROC curve

Table 1

Independent predictors of 6-month mortality after hospitalization with ACS

Factor	ОШ	95% ДИ	p
Non-prescription of aspirin at discharge	5,883	2,302-15,035	<0,0001
Newly diagnosed heart failure, pulmonary edema or shock in a hospital	5,734	2,585-12,717	<0,0001
Age ⩾75	5,328	2,697-10,597	<0,0001
Non-prescription of beta-blocker at discharge	4,984	2,297-10,815	<0,001
In-hospital management of ACS without immediate PCI (primary PCI during ST-segment elevation ACS or PCI during the first 72 hours in non-ST-segment elevation ACS)	3,902	1,559-9,770	0,004
Serum creatinine upon admission ⩾100 μmol/L	3,091	1,555-6,144	0,001
Body mass index <30 kg/m^2	2,788	1,236-6,292	0,014

Abbreviations: OR — odds ratio, CI — confidence interval, PCI — percutaneous coronary intervention.

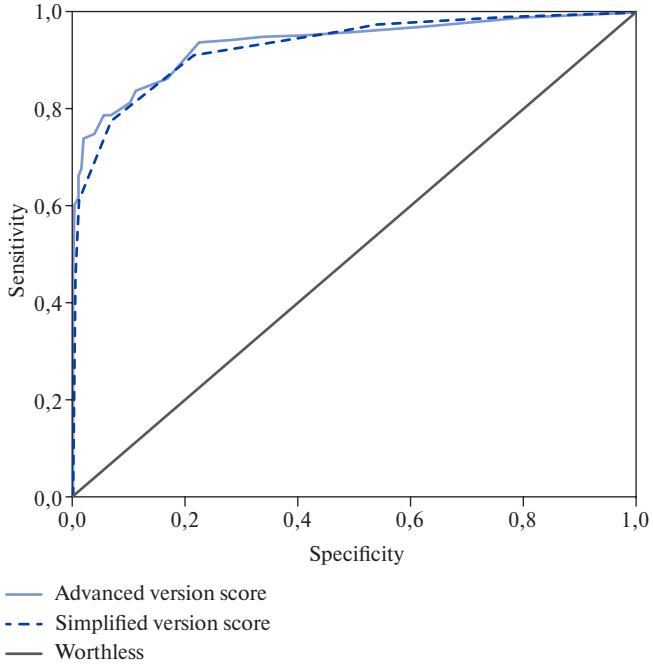

Figure 1. ROC curves for advanced and simplified versions of RECORD-6 score.

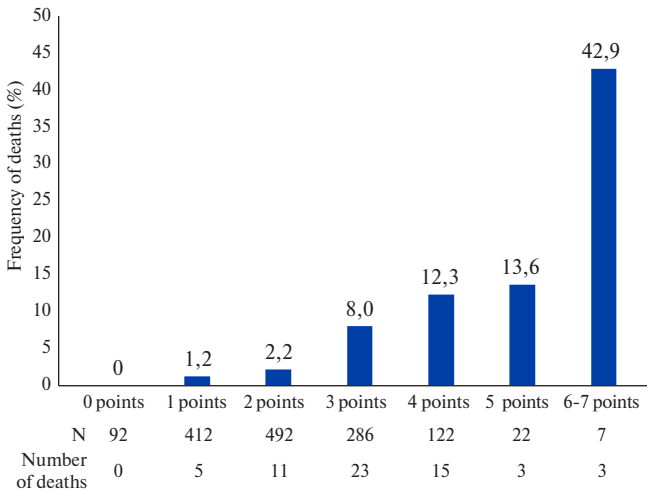

Figure 2. The relationship of the values on the RECORD-6 score with 6-month post-ACS mortality.

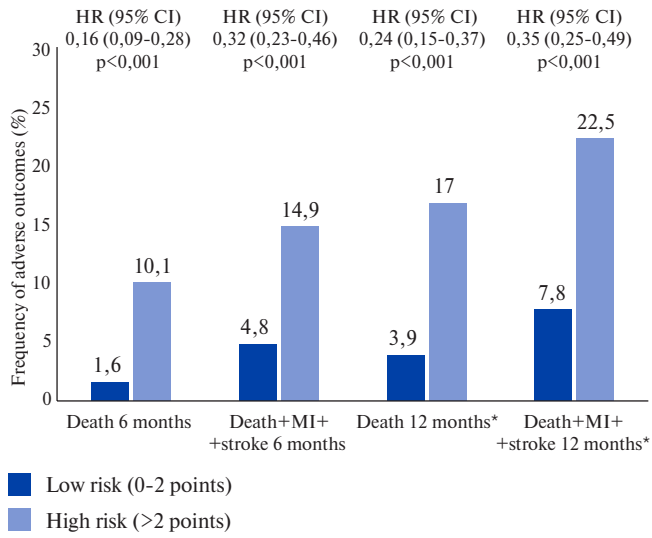

Figure 3. The incidence of long-term adverse events in low- and high-risk patients according to the RECORD-6 score.
Note: * — in patients with outcomes recorded after 12 months (n=966).
Abbreviations: HR — hazard ratio, CI — confidence interval, MI — myocardial infarction.

analysis, it has the best proportion of prognostic sensitivity and specificity. Thus, the value of <3 points indicates a low risk of long-term adverse events, and the value of ⩾3 points — high risk. The incidence of adverse events in patients with high and low risk according to the RECORD-6 score is presented in Figure 3.

It can be seen that the high risk on the RECORD-6 score was associated with a significantly higher rate of 6- and 12-month mortality after hospitalization, as well as serious adverse events (death, myocardial infarction or stroke) over the same period of time.

Figure 4 and Table 3 show a comparison of the prognostic values of the RECORD-6 and the 6-month GRACE risk score, expressed as the area under the ROC curve. Although the area under the ROC curve was visually larger for the RECORD-6 score (espe-

Table 2

Factors and their values for the novel RECORD-6 score

	Factor	Score
Data on admission or close to admission	Body mass index <30 kg/m^2	1
	Age ⩾75	1
	Serum creatinine upon admission ⩾100 μmol/L	1
In-hospital events	In-hospital management of ACS without immediate PCI (primary PCI during ST-segment elevation ACS or PCI during the first 72 hours in non-ST-segment elevation ACS)	1
	Newly diagnosed heart failure, pulmonary edema or shock in a hospital	1
Prescriptions at discharge	Non-prescription of beta-blocker at discharge	1
	Non-prescription of aspirin at discharge	1
Maximum score		7

Abbreviations: OR — odds ratio, CI — confidence interval, PCI — percutaneous coronary intervention.

Table 3

Areas under the ROC curves of the RECORD-6 and the 6-month GRACE risk score

	Area under the ROC curve	95% CI	p
All patients			
RECORD-6	0,872	0,847-0,909	0,47
6-month GRACE risk score	0,832	0,796-0,868	
Patients with non-ST-segment elevation ACS			
RECORD-6	0,822	0,770-0,874	0,70
6-month GRACE risk score	0,795	0,738-0,852	
Patients with ST-segment elevation ACS			
RECORD-6	0,931	0,897-0,964	0,46
6-month GRACE risk score	0,865	0,822-0,907	

Abbreviations: CI — confidence interval.

cially in ST-segment elevation ACS), this difference was not statistically significant.

Discussion

This analysis, based on the ACS RECORD-3 register (Russia) was performed, firstly, because of the obvious importance for assessing the risk of long-term adverse events after ACS, secondly, because of the rare practical use of prognostic scores for these purposes (even such accurate and well-validated as the GRACE score) [4, 5], and thirdly, due to the experience in creating the RECORD prognostic score [6]. This score showed a high accuracy in assessing the risk of in-hospital adverse events in patients with ACS, and can also be used for more targeted selection of patients with non-ST-segment elevation ACS for invasive coronary procedures.

The main idea for creating a new prognostic score was to evaluate the long-term prognosis in ACS patients surviving during hospitalization. Exclusion of patients not surviving during hospitalization made it possible to offset the significance of factors of early-stage unfavorable prognosis. The new score was developed according to the standard methodology, where independent predictors of an unfavorable outcome were identified and assigned the score components. As in the above-mentioned RECORD score, two versions of the new score were compared: the advanced one, where the "weight" of each factor was determined by its odds ratio value, and the simplified one, where each factor had the same "weight". Since the simplified version was not inferior to the advanced one in terms of prognostic sensitivity and specificity, it was chosen as a RECORD-6 score. Thus, the new score includes 7 various factors: old age, increased creatinine level, in-hospital management of ACS without immediate percutaneous coronary intervention (PCI), non-prescription of aspirin or beta-blocker, BMI <30 kg/m^2, in-hospital development of heart failure, shock, pulmonary edema.

It seems that there is no need to discuss in detail the individual prognostic value of each factor, especially taking into account that their combination (RECORD-6 score), showed high prognostic accuracy and the value of area under the ROC curve (0,931). Using the ROC analysis, a score of 3 was determined as a cut-off point, dividing the RECORD-6 score into low and high risk. The use of this cut-off point was highly accurate for predicting the 6-month and 12-month mortality rates, and the sum of events (all-cause mortality, myocardial infarction and stroke) after 6 and 12 months.

To assess the value of the RECORD-6 score, it was compared with the 6-month GRACE risk score by comparing the areas under the ROC-curves. Despite the quantitative advantage of the RECORD-6 score, this difference was not significant. It is noteworthy that the most marked advantage of the RECORD-6 score over the GRACE score was among patients with ST-segment elevation ACS. It should be noted that in the original sample of the GRACE register, on the basis of which the 6-month mortality risk score was developed, the accuracy, defined as the area under the ROC curve, was 0,81 [2]. This value is quite similar with the data obtained for GRACE score in our study (0,795). This may indirectly indicate that the patients of the RECORD-3 register are quite typical and characteristic for the population of ACS patients. Therefore, the novel RECORD-6 score is at least no worse than the GRACE score and can be used in clinical practice.

Study limitations. The current analysis has the following limitations:

1) Creating a new prognostic score was not the primary aim of the ACS RECORD-3 register;

2) The results obtained require validation in other independent cohorts of patients with ACS;

3) To use the RECORD-6 score in clinical practice, additional studies and its validation in other cohorts of patients with ACS are required.

Conclusion

1) Based on the ACS RECORD-3 register (Russia), a new risk score for predicting the 6-month all-cause mortality after hospitalization with ACS was created;

2) The novel RECORD-6 score includes 7 components (independent predictors of 6-month mortality after ACS): 1) body mass index <30 kg/m^2, 2) age ⩾75 years, 3) serum creatinine upon admission ⩾100 μmol/L, 4) in-hospital management of ACS without immediate PCI (primary PCI during ST-segment elevation ACS or PCI during the first 72 hours in non-ST-segment elevation ACS), 5) newly diagnosed heart failure, pulmonary edema or shock in a hospi-

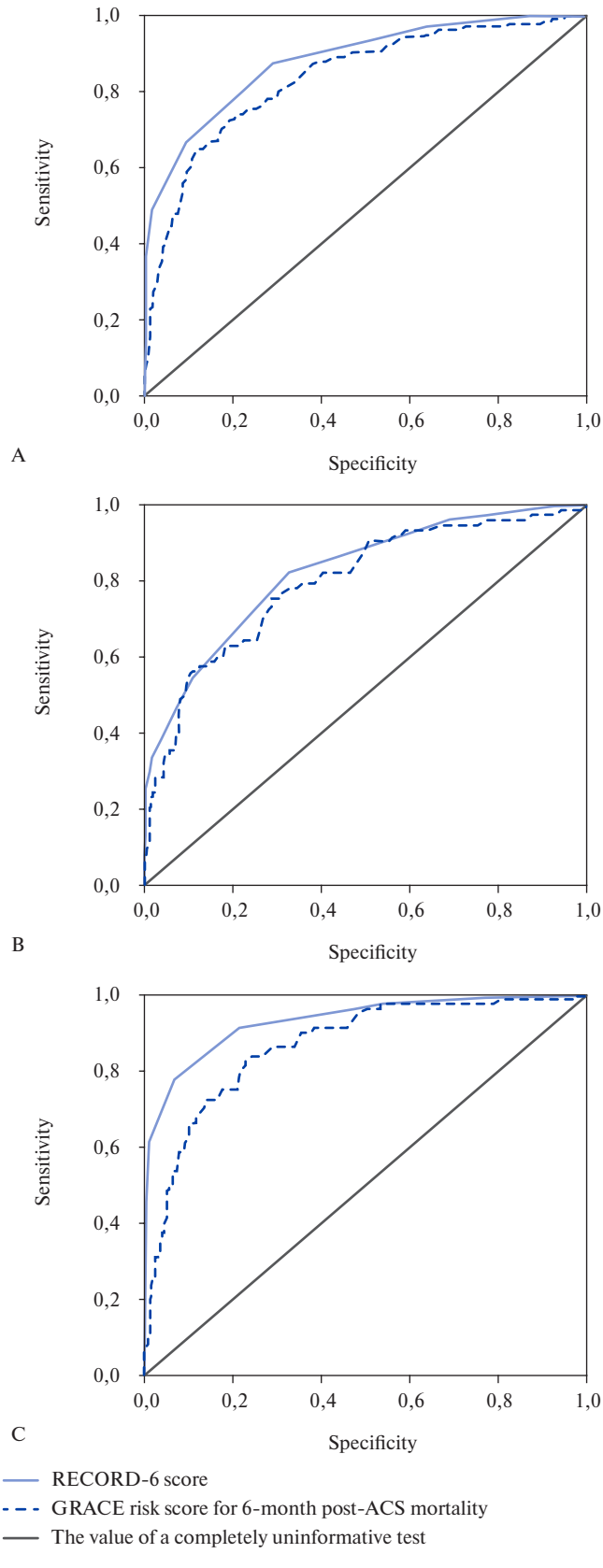

Figure 4 (A, B, C). ROC curves of the RECORD-6 score and the 6-month GRACE risk score for 6-month post-ACS mortality for all patients (**A**), patients with non-ST-segment elevation ACS (**B**) and ST-segment elevation ACS (**C**).

tal, 6) non-prescription of aspirin at discharge; and 7) non-prescription of beta-blocker at discharge;

3) Relative to the GRACE risk score for 6-month mortality, the prognostic value of the RECORD-6 score is at least no worse.

4) A score of 3, considered as a cut-off point, allows accurately dividing the patients into low and high risk groups in relation to 6- and 12-month mortality, as well as predicting the sum of events (all-cause mortality, myocardial infarction and stroke) after 6 and 12 months of the ACS onset.

Relationships and Activities: not.

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Cardiac strain in right ventricular myocardial infarction and pulmonary embolism

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Aim. To study the prospects of using parameters of right ventricle (RV) longitudinal strain (LS) during systole for the differential diagnosis of RV myocardial infarction (RVMI) and pulmonary embolism (PE).

Material and methods. The study included 83 patients who were hospitalized with RVMI or PE in the period from December 2017 to May 2019. The study of RV LS using the two-dimensional speckle-tracking echocardiography was carried out in 30 patients with RVMI (group 1), 15 patients with high-risk PE (group 2), and 38 patients with intermediate-risk PE (group 3).

Results. The mean values of RV global LS in patients of groups 1 and 2 did not differ (12,8±2,69 and 12,0±2,56%, respectively) and were significantly lower than in patients of group 3 (15,9±3,03%). The ratio of the interventricular septum (IVS) LS to the RV free wall (FW) LS in the group 1 (1,04±0,43) was significantly lower than in the groups 2 (1,61±0,52) and 3 (1,29±0,38). The ratio of the LS of the RVFW basal segment to the apical segment in group 1 (0,60±0,37) was also significantly lower than in groups 2 (1,69±1,57) and 3 (1,67±1,33).

Conclusion. In patients with RVMI, there is a comparable decrease in the LS of the RVFW and IVS, and the LS of the basal segment decreases to a greater extent than the apical one. In patients with PE, the decrease in the LS of the RVFW is more pronounced than in IVS, and the LS of the apical segment decreases to a greater extent than the basal one. These differences can be used for the differential diagnosis of RVMI and PE.

Key words: right ventricular strain, right ventricular myocardial infarction, pulmonary embolism.

Relationships and Activities: not.

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According to the 2019 ESC guidelines [1], echocardiography is the method of choice in patients with suspected pulmonary embolism (PE)-related shock. If computed tomographic pulmonary angiography (CTPA) is not possible, identification of right ventricle (RV) overload is sufficient for diagnosis of PE. Nevertheless, the guidelines note that for the differential diagnosis of RV myocardial infarction (RVMI) and PE, additional echocardiographic criteria can be required.

The reason for this reservation was a study by Casazza F, et al. [2], which showed that the McConnell sign does not allow to differentiate RV dysfunction caused by pressure overload from dysfunction associated with reduced blood supply. The authors noted that differences in pulmonary arterial pressure also do not always allow differentiating RVMI and high-risk PE. This because in the first case left ventricular (LV) dysfunction can be accompanied by a noticeable increase in pulmonary blood pressure, and in the second, due to severe RV dysfunction, pulmonary arterial pressure may be relatively low. In addition, studying of critically ill patients showed that it is often not possible to obtain the visualization quality needed to accurately assess the tricuspid pressure gradient.

Taking all these points together, it seems relevant to study the possibilities of using speckle-tracking echocardiography for differential diagnostics of RVMI and PE.

The aim of the study was to compare the parameters of longitudinal systolic strain in patients with RVMI and PE.

Material and methods

The study included 83 patients who were hospitalized in the Tver Regional Clinical Hospital from December 2017 to May 2019. This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committee of Tver State Medical University approved this study. All patients signed informed consent.

Group 1 consisted of 30 patients with RVMI and related shock. There were following diagnostic criteria for RVMI: 1) right coronary artery (RCA) occlusion on coronary angiography, 2) RV dilatation on echocardiography performed at hospital admission (Philips CX50), 3) ST-segment elevation in leads V3R and V4R. All patients with RVMI underwent primary percutaneous coronary intervention with stent implantation in the RCA.

The diagnosis of PE was verified by CTPA. Group 2 consisted of 15 patients with PE and related shock (high-risk PE). Group 3 included 38 patients with signs of RV overload, but without severe systemic hemodynamic impairment (intermediate-risk PE, group 3).

Echocardiography (Vivid S70, GE) in patients of the 1st and 2nd groups was carried out on the first day after hemodynamic stabilization; in patients of group 3 — on one day with CTPA. RV diastolic dimension was measured in the longitudinal parasternal view, and tricuspid annular plane systolic excursion (TAPSE) in the four-chamber view. Pulmonary artery systolic pressure (PASP) was estimated by tricuspid regurgitation velocity. Visualization and estimation of ultrasound parameters were performed in accordance with ASE and EACVI guidelines [3].

To assess the RV longitudinal systolic strain by two-dimensional speckle-tracking echocardiography (2DSTE), in accordance with consensus document [4, 5], RV-focused four-chamber view was used with determination of basal, middle, and apical longitudinal strain of RV free wall (RVFW) and interventricular septum (IVS). According to EACVI/ASE guidelines [3, 6], absolute strain values were used. The global RV strain was calculated as the average strain for all six RV segments, the RVFW and IVS strain — as the average strain of the three related segments. The ratio of IVS and RVFW strain (IVS/RVFW), as well as basal and apical strain of the RVFW (B/A RVFW) and IVS (B/A IVS) were estimated.

In statistical processing, the mean and standard deviation were calculated. The significance of intergroup differences was determined using univariate analysis of variance and evaluated using the Newman-Keuls test. Frequency analysis was performed with chi-squared test and Bonferroni correction for multiple intergroup comparisons. Intergroup differences were considered significant with a probability of α error <5%. To determine the cut-off points of patients with RVMI and PE, we used a receiver operating characteristic (ROC) analysis.

Results

Table 1 shows that patients with RVMI (group 1) and pulmonary embolism (groups 2 and 3) were comparable in age, but the male proportion among RVMI patients was higher than among PE patients. The incidence of hypertension and diabetes was the same in all groups. Risk factors for pulmonary embolism, such as a history of venous thromboembolism, recent surgery or trauma, chronic lung diseases, and cancer, were rare in patients with RVMI and, in most cases, have occurred in patients with PE.

At the time of the examination, the levels of systolic blood pressure in patients of the 1st and 2nd groups did not differ and was significantly lower than in the 3rd group. Tachycardia and reduced oxygen

Table 1

Clinical characteristics of patients

Parameter	Group 1 (n=30)	Group 2 (n=15)	Group 3 (n=38)
Age, years	61,8±10,9	57,2±16,0	59,7±14,9
Men, n (%)	27 (90,0)	8 (53,3)[1]	22 (57,9)[1]
Hypertension, n (%)	19 (63,3)	8 (53,3)	19 (50,0)
Diabetes, n (%)	5 (16,7)	3 (20,0)	5 (13,2)
Risk factors for PE, n (%)	4 (13,3)	10 (66,7)[1]	24 (63,2)[1]
SBP, mm Hg	105,8±16,4	99,5±25,9	128,7±18,8[1,2]
HR >100 bpm, n (%)	5 (16,7)	10 (66,7)[1]	9 (24,3)[2]
SpO_2 <90%, n (%)	2 (6,7)	11 (73,3)[1]	8 (21,6)[2]
PASP, mm Hg	32,6±5,5	64,3±12,8[1]	59,6±19,0[1]
RV dimension, cm	3,70±0,39	3,71±0,54	3,55±0,49
TAPSE, cm	1,18±0,22	1,28±0,33	1,64±0,39[1,2]

Notes: data are presented as the mean and standard deviation or as absolute and relative values. [1,2] — significant differences with the 1st and 2nd group.

Abbreviations: PE — pulmonary embolism, SBP — systolic blood pressure, HR — heart rate, SpO_2 — blood oxygen saturation, PASP — pulmonary artery systolic pressure, RV — right ventricle, TAPSE — tricuspid annular plane systolic excursion.

Table 2

Data on myocardial strain

Parameter	Group 1 (n=30)	Group 2 (n=15)	Group 3 (n=38)
RV global strain, %	12,8±2,69	12,0±2,56	15,9±3,03[1,2]
Total RVFW strain, %	12,7±3,44	9,64±2,76[1]	14,6±4,48[2]
• basal, %	9,53±4,56	10,8±4,83	17,2±5,51[1,2]
• middle, %	12,2±4,67	9,60±3,09	15,1±5,14[1,2]
• apical, %	16,8±4,09	8,93±4,45[1]	12,5±4,72[1,2]
Total IVS strain, %	12,2±2,83	14,7±3,22[1]	17,3±2,69[1,2]
• basal, %	9,47±3,08	13,9±4,42[1]	17,9±3,54[1,2]
• middle, %	11,2±3,13	15,5±3,91[1]	18,7±3,57[1,2]
• apical, %	17,0±5,57	14,1±5,32	15,2±3,68
IVS/RVFW	1,04±0,43	1,61±0,52[1]	1,29±0,38[1,2]
B/A RVFW	0,60±0,37	1,69±1,57[1]	1,67±1,33[1]
B/A IVS	0,64±0,382	1,20±0,73[1]	1,27±0,45[1]

Notes: data are presented as the mean and standard deviation or as absolute and relative values. [1,2] — significant differences with the 1st and 2nd group.

Abbreviations: RV — right ventricle, RVFW — right ventricle free wall, IVS — interventricular septum, IVS/RVFW — the ratio of the IVS strain to the RVFW strain, B/A — the ratio of the basal strain to the apical.

saturation were observed in most patients of the 2nd group, in a quarter of group 3 patients, and in some cases in the 1st group. PASP >30 mm Hg were in 15 (50,0%) patients with RVMI and in all patients with PE. Moreover, PASP in patients with PE was on average 2 times higher than in patients with RVMI. RV dilatation was observed in all patients, a TAPSE decrease ⩾1,7 cm — in all patients of the 1st and 2nd group and 25 (65,8%) patients of the 3rd group. The average values of RV dimension and TAPSE in the 1st and 2nd groups were almost the same; in the 3rd group, RV dimension was slightly lower (p>0,05), and the TAPSE was significantly higher than in groups 1 and 2.

The average values of RV global strain in 1st and 2nd groups were lower than in 3rd group and did not differ from each other (Table 2). However, in the 1st group, the average values of IVS and RVFW strains were almost equal to each other, and their ratio was close to 1. In the 2nd group, the IVS/RVFW ratio was

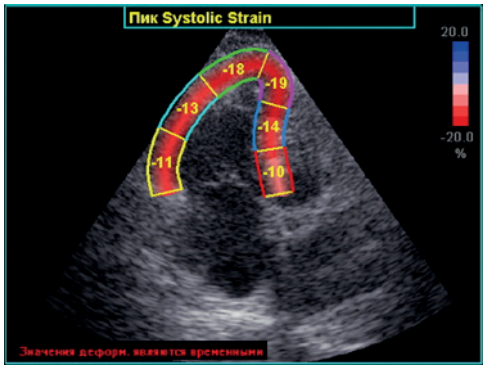

Figure 1. RV myocardial strain in a patient with RVMI.
Note: the global strain is 14,2%; the RVFW strain (14,0%) is comparable with the IVS strain (14,3%); the RVFW strain is reduced from the apical segments to the basal; the ratio of the basal strain to the apical is 0,61.

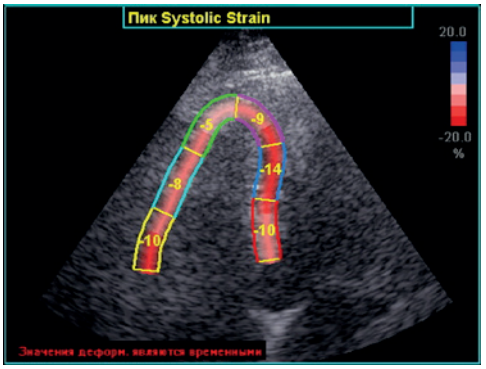

Figure 2. RV myocardial strain in a patient with PE.
Note: the global strain is 9,3%, the RVFW strain (7,4%) is 1,5 times less than the IVS strain (11,0%); the RVFW strain decreases from the basal segments to the apical; the ratio of the basal strain to the apical is 2,0.

1,61, and in the 3rd group — 1,29. Thus, a decrease of RV global strain in patients with PE is associated, first of all, with a decrease in RVFW strain, while in patients with RVMI — equally with IVS and RVFW decrease.

According to ROC analysis, the cut-off point for patients with RVMI and PE is IVS/RVFW value of 1,18 (area under the curve — 76,5%). The sensitivity of the criterion is 70%, the specificity — 80%.

In patients with RVMI, RVFW strain decrease from apical segments to basal ($p<0,001$), and in patients with PE — from basal to apical segments ($p<0,001$). As a result, the B/A RVFW ratio in patients with RVMI was on average 0,60, and in patients with PE — 1,68. The cut-off point of patients with RVMI and PE is the B/A RVFW ratio of 0,94 (area under the curve — 90,2%). The sensitivity of this criterion is 89%, the specificity — 87%.

In patients with RVMI, both IVS and RVFW strains decrease from apical to basal segments ($p<0,001$), as a result of which the B/A IVS ratio was 0,64. In patients with PE, the average values of the IVS basal and middle strains do not differ and exceed the apical strain ($p<0,01$), as a result of which the B/A IVS ratio was 1,25. The cut-off point of patients with RVMI and PE is the B/A IVS of 0,85 (area under the curve — 88,6%). The sensitivity of the criterion is 79%, the specificity — 87%.

It should be noted that the B B/A IVS correlates both with the B/A RVFW ($r=0635$, $p<0,0001$) and the IVS/RVFW ($r=0662$, $p<0,001$). However, there is no correlation between the B/A RVFW and the IVS/RVFW ($r=0,18$, $p>0,05$), which allows them to be used as part of the combined criterion for the PE diagnosis. At least one of the considered signs (IVS/RVFW $\geqslant$1,18 or B/A RVFW $\geqslant$0,94) was observed in 52 (98,1%) patients with PE and only 13 (33,3%) patients with RVMI. The sensitivity of this criterion for PE diagnosis approaches 100%, which allows to rule out this pathology if the patient does not have any of the listed signs. Both of these signs were detected in 32 (60,4%) patients with PE and none of the patients with RVMI, which indicates 100% specificity of this combination for RV pressure overload and allows diagnosing PE.

Thus, in patients with RVMI, a decrease in RV global strain is equally associated with a decrease in RVFW and IVS strains. Moreover, RV basal strain decreases to a greater extent than the apical (Figure 1). In patients with PE, a decrease in RV global strain is associated mainly with RVFW strain decrease and, to a much lesser extent, with IVS strain decrease. In PE, RV apical strain decreases to a greater extent than the basal (Figure 2). The revealed differences in RV strain can be used for the differential diagnosis of RVMI and PE.

Discussion

According to the literature data, the average RV global strain in healthy individuals is 24,3% [5], in patients with RVMI — 13,7% [7], and with PE — 13,1-17,2% [8-10]. In this study, close data were obtained both in patients with RVMI (12,8%) and PE (12,0-15,9%). However, the literature data on strain of various parts of the RV are not fully consistent with the results of this study. According to study by Platz E, et al. [11], IVS strain in healthy people is on average less than the RVFW strain (18,5 vs 24,9%). Study by Park SJ, et al. [7] showed the same ratio in patients with RVMI (13,5 vs 15,1%). However, according to the present study, the average values of the IVS and RVFW strains in patients with RVMI did not differ (12,2 and 12,7%).

In RVMI, the IVS/RVFW ratio reflects the severity of damage due to RCA occlusion. In the acute period, this ratio depends on the ischemic areas of IVS and RVFW, later on necrotic area. RVFW myocardium receives blood not only through the coronary arteries, but also through the thebesian arteries, as a result of which the reduced blood supply through RCA leads not so much to the myocytes' death as to their hibernation [12, 13]. Improving blood supply leads to the restoration of myocardial contractility and an increase in the RVFW strain, as a result of which the IVS/RVFW ratio decreases.

In this study, the assessment of myocardial strain in patients with RVMI was carried out on the first day after revascularization, and in the study by Park SJ, et al. [7] — in the first three days. This can explain the lower values of the RVFW strain (12,7 vs 15,7%) and the higher IVS/RVFW ratio (1,04 vs 0,89) in the current paper. It can be assumed that in the early stages, patients with extensive RV lesion have IVS/RVFW ratio significantly higher than 1, which is typical for PE. This is probably the reason for the low specificity (80%) of IVS/RVFW ratio as a criterion for PE diagnosis.

The second feature of myocardial strain in patients with RVMI is the predominance of the RVFW apical strain over the basal, while in healthy individuals, the RVFW strain decreases from basal segments to apical: 26,5, 25,7, and 21,5% [7]. The decrease of the basal and middle strain in RVMI is due to RCA supplies blood only to the basal and middle segments of RVFW and IVS, while apical segments receive blood from the left anterior descending artery. Obviously, the earlier the examination is carried out, the more the RVFW strain decreases and, as a result, the lower the ratio of the basal and apical strains. As the contractility of the basal segments of the RVFW is restored, this ratio increases, but, as a rule, does not reach the values observed in PE. This explains the rather high specificity (87%) of the second criteria for PE diagnosis that we proposed (B/A RVFW $\geqslant$0,94).

The decrease in RV strain in PE patients is associated not with ischemic lesion, as in RVMI, but with RV pressure overload and related dilatation. Dilation is accompanied by diastolic hyperextension of the myocardium, which reduces the longitudinal systolic strain, necessary for ejection of stroke volume. At the global level, this is manifested by a TAPSE decrease, at the myocardial level — by a strain decrease [14, 15].

It can be assumed that thin RVFW stretches more easily than IVS, and as a result of RV dilatation, the RVFW strain decreases to a greater extent than the IVS strain. Indeed, according to Descotes-Genon V, et al. [9], in PE patients without RV overload, the IVS strain, as normal, is less than the RVFW strain (17,2 vs 20,2%), and when the RV is overloaded, the IVS/RVFW ratio changes to the opposite: 13,5 vs 12,7%. The same IVS/RVFW ratio in patients with RV overload was revealed in study by Platz E, et al. [11] (15,0 vs 14,2%) and in the present study.

The ratio of RVFW basal and apical strains remains the same as in healthy people. According to study by Vitarelli A, et al. [8], the RVFW apical strain in healthy individuals is 1,23 times less than the basal (26,5 vs 21,5%), and in patients with PE — 1,22 times (19,1 and 15,6%). Similar ratio was found in the studied patients with PE.

Conclusion

The RV global strain is reduced both in patients with RVMI and PE. However, with RVMI, there is a comparable decrease of longitudinal strain in RVFW and IVS, while with PE, the decrease in RVFW strain is much more pronounced than in IVS strain. In addition, patients with RVMI have a decrease in RV strain from the apical segments to the basal, and in patients with PE, from the basal to the apical. The revealed differences can be used for the differential diagnosis of RVMI and PE.

Relationships and Activities: not.

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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

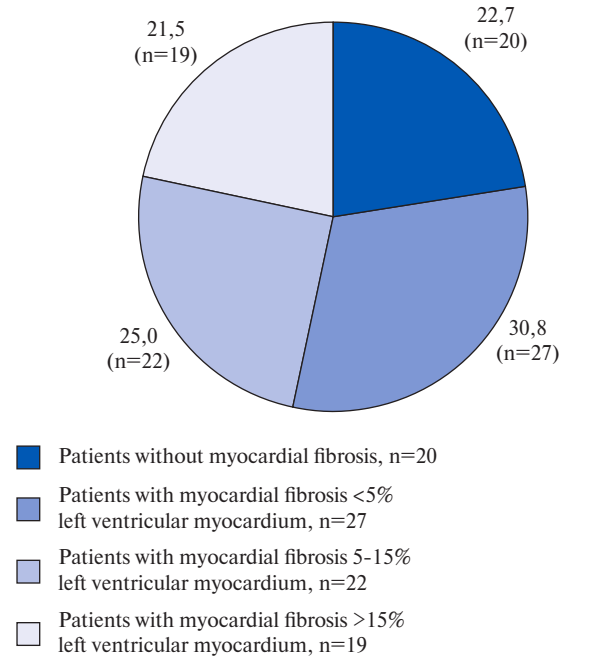

Figure 1. The extent of cardiac scarring in patients with CAD 1 year after MI.

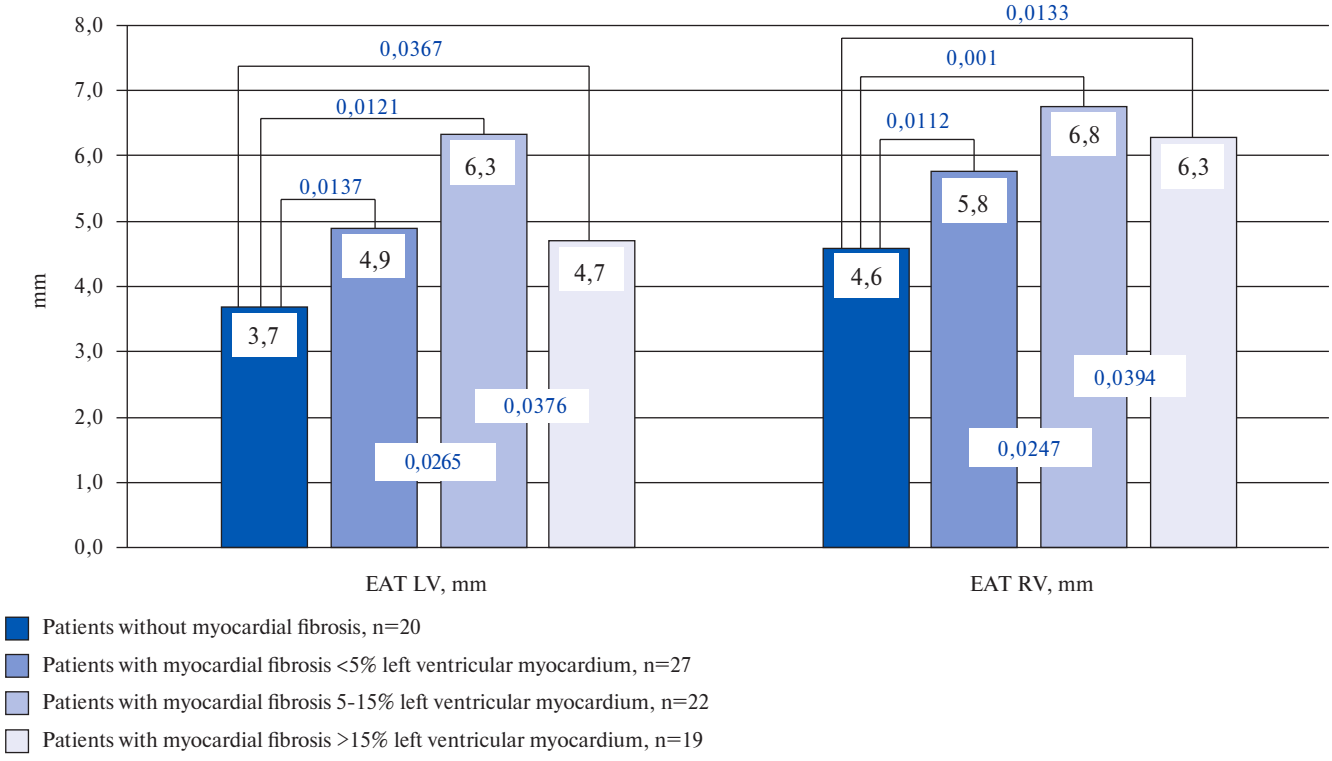

Figure 2. The EAT thickness depending on the presence of cardiac fibrosis 1 year after myocardial infarction.

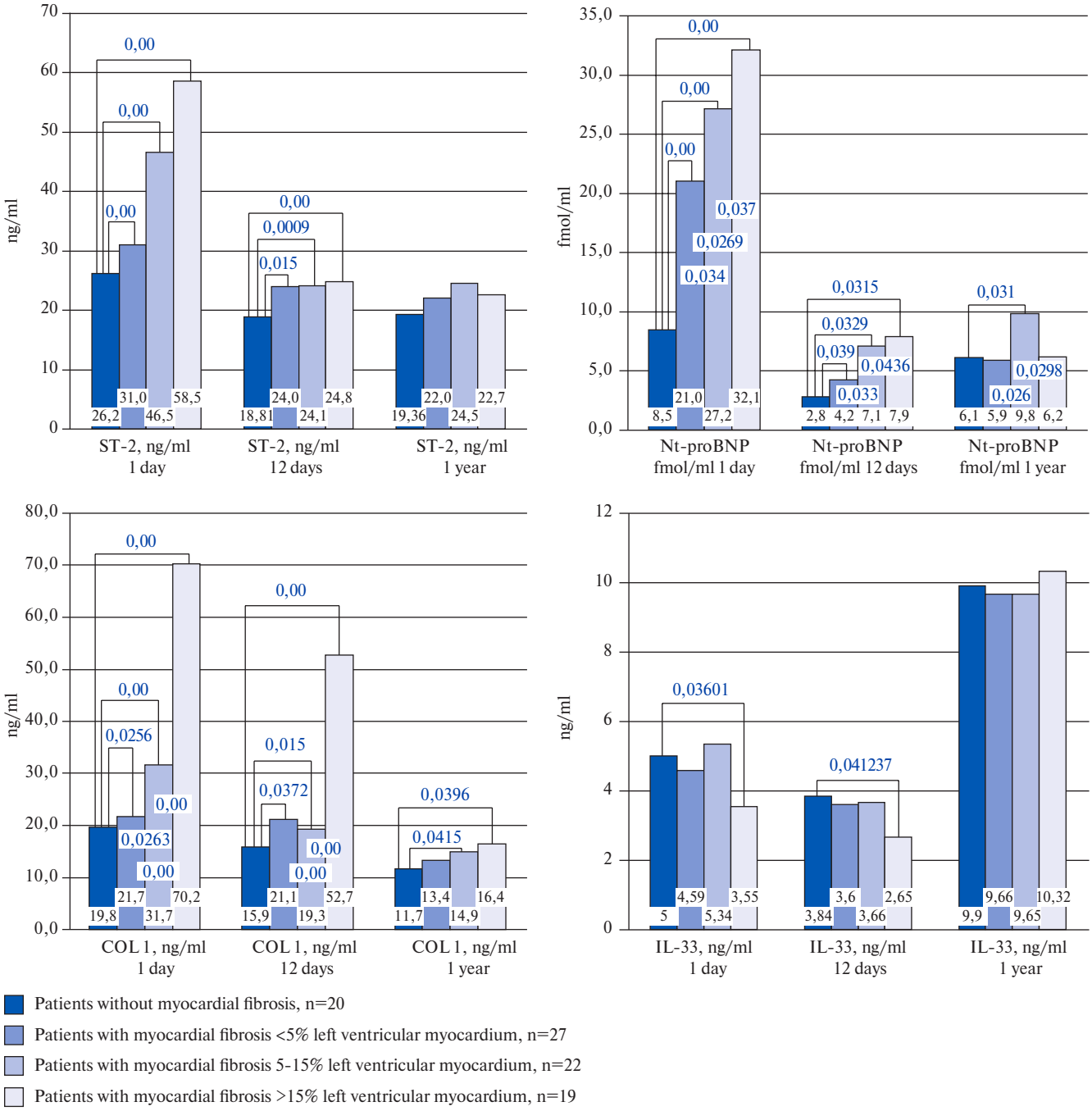

Figure 3. Biochemical parameters during and after hospitalization depending on the extent of cardiac fibrosis.

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.

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].

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.

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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Levels of proprotein convertase subtilisin/kexin type 9 in patients with acute myocardial infarction

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Aim. To study the levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) in patients with acute myocardial infarction (MI).

Material and methods. The study included 74 patients with acute MI. PCSK9 was determined by enzyme-linked immunosorbent assay.

Results. The mean PCSK9 levels were 479,7±15,4 ng/ml. No significant correlation was found between PCSK9 and total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides. In the group of smokers, a significant inverse correlation was found between the levels of PCSK9 and HDL-C (-0,45; p=0,039). In the group of patients with body mass index <25 kg/m^2, a significant inverse correlation of PCSK9 levels with total cholesterol (-0,45, p=0,008), HDL-C (-0,42; p=0,029) and LDL-C (-0,47; p=0,003) was found.

Conclusion. In patients with MI, a correlation of PCSK9 levels with lipid profile was found in smokers, as well as in patients with a low body mass index.

Key words: proprotein convertase subtilisin/kexin type 9, myocardial infarction.

Relationships and Activities: not.

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Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a hydrolase enzyme that binds to the low-density lipoprotein receptor. This leads to its degradation in endosomes and lysosomes and increases the level of low-density lipoprotein cholesterol (LDL-C) in the blood serum. There are a number of studies on the correlation of PCSK9 levels and coronary artery disease (CAD). In a study of 4232 healthy men and women with 15-year follow-up, the authors revealed a significant direct relationship between the PCSK9 level and cardiovascular events [1]. In a study by Caselli C, et al. of 412 patients with stable CAD, PCSK9 plasma levels was an independent predictor of coronary atherosclerosis severity [2].

In a study by Dalgic Y, et al. of 168 patients with non-ST segment elevation acute coronary syndrome, PCSK9 levels was an independent predictor of a high SYNTAX score [3]. The use of PCSK9 inhibitors in the acute myocardial infarction (MI) is currently a debatable issue [4]. The aim of this study was to assess the PCSK9 levels in patients with MI.

Material and methods

The study included 74 patients with MI confirmed by generally accepted criteria: cardiac troponin I increase; typical clinical picture; characteristic electrocardiography (ECG) changes; coronary angiography data. There were following inclusion criteria: acute MI; age of patients 40-70 years, signed informed consent. The exclusion criteria were: age over 70 years; not signed informed consent; circulatory failure; cerebrovascular accident in last 6 months prior to inclusion; severe kidney (creatinine >160 μmol/L) and liver failure (transaminase levels ⩾3 times the normal range); any heart rhythm disorders requiring treatment; second- and third-degree atrioventricular block; bradycardia (⩽50 bpm); sinoatrial block; respiratory failure (⩾II degree); ineffective contraception in women of reproductive age; pregnancy and lactation; alcoholism and drug addiction; history of cancer.

Upon hospital admission, we determined levels of troponin I, brain natriuretic peptide, lipids and glucose. Complete blood count, ECG, body mass index (BMI), smoking profile and Gensini score estimated by coronary angiography were also assessed. Blood levels of PCSK9 were determined using the Human PCSK9 ELISA kit (BioVendor, Czech Republic); blood samples were frozen at -70° C.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The local medical ethics committee approved this study.

Statistical analysis methods. Normality of distribution was determined using the Shapiro-Wilk test. To describe normally distributed quantitative traits, the arithmetic mean (M) and the standard deviation (σ) were considered as M±σ. To describe the sampling distribution of non-normally distributed quantitative traits, we used the median (Me), lower (25%) and upper (75%) quartiles (Q1 and Q3) as Me [Q1; Q3]. The statistical significance of quantitative trait differences was evaluated by the nonparametric Mann-Whitney U test. To identify the association between the PCSK9 level and other quantitative variables, nonparametric Spearman's correlation analysis was used.

Table 1
Blood levels of PCSK9 in patients with MI

	PCSK9 levels (ng/ml) M±σ Me [Q_1; Q_3]	p (between subgroups of men and women)
General group (n=74)	479,7±15,4 466,0 [378,0-582,8]	
Men (n=59)	465,6±16,2 461 [375,5-556,5]	
Women (n=15)	534,9±38,9 515 [441,5-658,0]	0,122

Results

The study included 74 patients: 59 (79,7%) men aged 58 years (interquartile range: 52-64 years old), 15 (20,3%) women aged 63 years (interquartile range: 62-65 years old). Forty-three patients had Q-wave MI.

Blood levels of PCSK9 in all patients and depending on the gender are presented in Table 1. There was no statistically significant difference between the PCSK9 levels in men and women (p=0,122). The lowest PCSK9 level recorded in the group was 214 ng/ml, the highest — 786 ng/ml.

There was no statistically significant correlation of PCSK9 with levels of total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides. However, in the group of smokers (n=22), an inverse moderate correlation between PCSK9 and HDL-C was revealed (-0,45, p=0,039).

A significant correlation was found between PCSK9 levels and lipid metabolism parameters depending on BMI: in the group of patients with BMI <25 kg/m^2 (n=22), there was inverse correlation of PCSK9 with levels of total cholesterol (-0,45, p=0,008), HDL-C (-0,42, p=0,029) and LDL-C (-0,47, p=0,003).

Discussion

The study of PCSK9 is of great practical interest, since the effects of alirocumab and evolocumab on reducing its levels has been proved [5, 6].

In one study, the authors investigated the PCSK9 levels in men (44-73 years) in different population

subgroups, its relationship with cardiovascular risk factors and long-term 7-year unfavorable prognosis, where the mean level of PCSK9 was significantly lower [7] than in our study (131,1±4,2 ng/ml, median 119,8 ng/ml).

In another population-based study of men aged 25-45, the mean PCSK9 level was 325,9±141,97 ng/ml, the median and interquartile range — 300,19 ng/ml (240,20 ng/ml; 361,80 ng/ml); there were also higher variability (from 20,90 ng/ml to 1249,04 ng/ml) [8] than in our study.

High variability of PCSK9 levels was also observed in Dallas Heart Study: the minimum — 33 ng/ml, the maximum — 2988 ng/ml [9]. Perhaps this is due to the population specificity of the PCSK9 level.

Several researchers have identified differences in PCSK9 levels depending on gender and BMI. So, in the Dallas Heart Study, the PCSK9 level was higher in women than in men (517 ng/ml and 450 ng/ml, respectively) [8, 9], which was also noted in our study: 515 ng/ml in women, 461 ng/ml in men.

In a study by Zhu YM, et al., insulin, LDL-C, and triglycerides were independent predictors of high PCSK9 concentration, and BMI inversely correlated with PCSK9 level, which differs from our data [10].

In independent samples of young men without cardiovascular disease and with different smoking status, the authors found that the PCSK9 level was higher in smokers (339,49±139,86 ng/ml; 311,82 ng/ml (251,04; 369,78 ng/ml) than in the non-smokers (315,17±143,16 ng/ml; 286,16 ng/ml (229,91; 351,71 ng/ml) (p=0,011) [11]. In a study by Leander K, et al., it was demonstrated that smokers had higher PCSK9 levels in quartiles 3 and 4 than non-smokers [1]. In a population study by Ridker P, et al., association of PCSK9 protein with smoking status was not observed [12].

In the study of PCSK9 levels in patients with ST-segment elevation MI, the severity of atherosclerotic lesions was assessed using the Gensini, Jeopardy, and SYNTAX scores, and the authors determined that levels of PCSK9, total cholesterol, LDL-C, creatinine were independent predictors of high SYNTAX score [3]. In our study, the severity of coronary atherosclerotic lesions was assessed by Gensini score, and we did not find a relationship between the severity of coronary atherosclerosis and the PCSK9 levels. In the Swiss population of patients with acute coronary syndrome, PCSK9 levels reached 374±149 ng/ml [13].

The data obtained in our study characterize the levels of PCSK9, its distribution and relationship with other lipid metabolism parameters in patients with MI.

Conclusion

1. Patients with MI and BMI <25 kg/m^2 have a significant inverse correlation of PCSK9 values with levels of total cholesterol (-0,45, p=0,008), HDL-C (-0,42, p=0,029) and LDL-C (-0,47, p=0,003).

2. Smokers with MI have a significant inverse correlation between the levels of PCSK9 and HDL-C (-0,45, p=0,039, n=22).

Relationships and Activities: not.

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In-hospital changes of echocardiographic parameters and their relationship with the procollagen I C-terminal propeptide in patients with myocardial infarction and preserved left ventricle systolic function

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Aim. To study the changes of echocardiographic parameters and their relationship with the procollagen I C-terminal propeptide (PICP) during hospitalization of patients with ST-segment elevation myocardial infarction (STEMI) and preserved left ventricular (LV) systolic function.

Material and methods. A total of 120 (100%) patients hospitalized with STEMI were examined. Upon admission, all patients underwent standard examinations to verify myocardial infarction (MI), including coronary angiography and, if necessary, coronary stent implantation. The mean values of LV ejection fraction (LVEF) were 40-49% in 3 patients (2,5%), <40% — in 31 patients (26%), LVEF was. We also analyzed patients with LVEF ⩾50%, n=86 (71,6%); mean age was 57,8 years. During the hospitalization, all patients received standard therapy; on the 1st and 12th day of MI, the PICP levels in venous blood serum was determined by enzyme-linked immunosorbent assay. In order to compare PICP values, a control group of healthy volunteers n=20 (100%) was formed, which were comparable by gender and age. In this group, the concentration of PICP was 179,2 [163.5; 194.9] ng/ml.

Results. By the 12th day, a significant decrease in the following parameters of the transmitral flow was revealed: DT (p=0,049), dE (0,012), Em (0,029), Em/ Am (p=0,000), Em/ early mitral flow propagation velocity (Vp) (p=0,001). This indicates diastolic function deterioration. At the same time, by the end of hospitalization, systolic function deterioration was recorded in 15,1% of cases. Initially, a higher PICP on the 1st day relative to the control group tended to decrease the concentration by the 12th day, but the differences did not reach statistical significance (p=0,466). Correlation analysis showed a relationship between PICP and echocardiography (Tei index, p=0,026, and mitral annulus velocity, p=0,049).

Conclusion. At the hospital stage of treatment of patients with STEMI and preserved LVEF, a negative changes of echocardiography parameters characterizing diastolic dysfunction was revealed. Positive correlation was established between the concentration of PICP with mitral annulus velocity and the Tei index, indicating an association between myocardial fibrosis and diastolic dysfunction.

Key words: myocardial infarction, markers of fibrosis, diastolic dysfunction.

Relationships and Activities: not.

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For many decades, cardiovascular diseases (CVD) have been one of the main causes of disability and high mortality among the working-age population [1-3]. In addition, the incidence of ST-segment elevation myocardial infarction (STEMI) increase among young population, more often men [4-6]. Heart failure (HF), as the most common late complication of myocardial infarction (MI), is increasingly progressing in patients with preserved myocardial contractility [7]. It was proved that during the first year after MI, mortality from left ventricular (LV) diastolic dysfunction (DD) ranges from 5-8%, and after 5 years, it is comparable with the mortality rate in patients with systolic HF [8]. LV myocardial fibrosis is considered as one of the most significant mechanisms for the development and progression of DD. Currently, much attention is paid to the study of serum markers of myocardial fibrosis, including collagen precursors. In particular, markers characterizing the activity of collagen synthesis and degradation are discussed [9]. Of particular note is procollagen I C-terminal propeptide (PICP) — precursor of type I collagen [10]. The issue remains open about the relationship of serum biomarkers of myocardial fibrosis with the echocardiographic parameters of cardiac structure, including after MI.

The aim of the study was to assess the changes of echocardiographic parameters and their relationship with the PICP during hospitalization of patients with STEMI and preserved LV systolic function.

Material and methods

Using the continuous sampling method, we included 120 (100%) patients with STEMI hospitalized for emergency indications for 7 months of 2015. There were following inclusion criteria: 1) an established diagnosis of STEMI (European Society of Cardiology (2015); 2) signed informed consent; 3) age >18 years; 4) Killip class I-III acute HF. There were following exclusion criteria: 1) clinically meaningful concomitant pathology; 2) acute coronary syndrome (ACS) as a complication of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); 3) age ⩾80 years; 4) Killip class IV acute HF; 5) death on the first day of hospitalization. The mean age of the sample was 57,8 years. There were 75,8% (n=91) of men and 24,2% (n=29) of women. All women were postmenopausal. In the hospital, all patients underwent standard laboratory and instrumental examinations to verify MI. Upon admission, all patients underwent coronary angiography (CA) using the Innova 3100 cath/angio system (General Electric, USA) and, if necessary, coronary stent implantation.

Echocardiography was performed using the Sonos 2500 ultrasound system (Hewlett-Packard, USA) (Russian HF Society, Russian Society of Cardiology, Russian Scientific Medical Society of Internal Medicine Guidelines (2018) for HF: chronic and acute decompensated. Diagnosis, prevention and treatment). The following parameters were determined: end-diastolic volume (EDV), end-systolic volume (ESV), end-diastolic dimension (EDD), end-systolic dimension (ESD), left (LA) and right atrial (RA) sizes, general myocardial contractility, state of heart valves, LV wall thickness, the presence and extent of dyskinesia in the areas of necrosis and scarring, aneurysm, papillary muscle damage and myocardial rupture zones according to the standard technique using one-dimensional and two-dimensional echocardiography, pulsed and continuous-wave Doppler echocardiography. The LV ejection fraction was calculated as EF=(LVEDV–LVESV/LVEDV)×100% (Simpson's rule). For the diagnosis of DD, we assessed following parameters of transmitral flow: ratio of peak velocity filling in early diastole (E) to atrial peak velocity filling (A-N=0,22-0,32 ms) (E/A-N ratio ⩾1), isovolumic relaxation time (IVRT), deceleration time (DT) of early diastolic filling estimated by pulsed Doppler echocardiography (N=160-220ms), early diastolic mitral annular velocity (e'), — ratio of E-wave over e'-wave (E/e' ratio), LV IVRT (IVRT-N=70-90 ms). The Tei index was calculated as IVCT+IVRT/ET (normal rate in adults <0,4). Increased values of this parameter reflect reduced systolic function; Tei index >1,0 are a sign of severe systolic and diastolic dysfunction.

In the study sample, LVEF of 40-49% were determined in three patients (2,5%). In 26% (n=31) of patients, LVEF was <40%. The final analysis was performed in patients with LVEF ⩾50%, n=86 (71,6%).

We determined serum PICP levels on the 1st and the 12th days of hospitalization by enzyme-linked immunosorbent assay using BCM Diagnostics kits (USA). During hospitalization, all patients received standard therapy in accordance with ESC guidelines (2015).

In order to compare the values of the studied markers, we formed control group of healthy volunteers (n=20) with comparable age (mean age 57,9 years) and gender (15 men (75%), 5 women (25%)). In the control group, the concentration of PICP was 179,2 [163,5; 194,9] ng/ml. Table 1 presents the clinical and medical history of the study sample.

The age of the patients was 59 [52; 64] years. We revealed high prevalence of cardiovascular risk factors: ~1/2 of patients were smokers; >2/3 of patients had a long-standing hypertension (HTN). In addition, hypercholesterolemia (21,6%) and carbohydrate

Table 1

Clinical characteristics of study patients

Parameter	n	%
Men	63	73,2
Women	23	27,7
Obesity (BMI ⩾30 kg/m^2)	24	28
Impaired carbohydrate metabolism	15	17,4
Current smoking	38	44,2
Former smoking	4	4,6
Hypertension	61	70,9
Hypercholesterolemia	18	21
Family history of coronary artery disease	3	3,5
Old myocardial infarction	3	3,5
Angina manifestations in history	27	31,4
Heart failure manifestations in history	10	11,6
Atrial fibrillation	2	2,3
Acute cerebrovascular accident (not earlier than 1 year before the study)	4	4,6
Peripheral artery disease	1	1,2
Chronic kidney disease	2	2,3
Percutaneous coronary intervention (not earlier than 1 year before the study)	2	2,3

metabolism disorders (18%) were also quite common.

Statistical processing was carried out using the software package Statistica 6.0. Independent groups were compared using the Mann-Whitney U test; dependent groups — Wilcoxon signed-rank test. The dependence between variables was determined by the Spearman's rank correlation coefficient. The differences were considered statistically significant at $p<0,05$.

Results

Echocardiography parameters on the 1st and 12th days were compared (Table 2). There was a significant increase of the LVEF ($p<0,001$) and LV stroke volume ($p<0,001$). At the same time, the ESD and ESV were decreased.

In a similar way, parameters of mitral flow were compared (Table 3). We revealed a significant decrease of following parameters: DT ($p=0,049$), dE (0,012), Em (0,029), Em/Am ($p<0,001$), Em/early mitral flow propagation velocity (Vp) ($p=0,001$).

On the 1st day, 25 (29,1%) patients with signs of DD were determined. On the 12th day, LVEF decrease <50% in 13 people (15,1%) and an increase in the number of patients with DD manifestations were identified.

There was a slight decrease in PICP levels on day 12 compared to day 1, however, the identified differences were not significant: 1st day — 605,0 (560,0; 670,0), 12th day — 602,0 (598,0; 625,0) ($p=0,466$). These values were significantly higher than in the control group (Figure 1).

Correlation analysis did not reveal the relationship between generally accepted echocardiographic parameters of LV diastolic function and PICP. Nevertheless, a relationship was found between PICP and echocardiographic parameters (Tei index and mitral annulus velocity), which can also characterize LV diastolic function (Figure 2). However, a direct comparison of the values of the Tei index and mitral annulus velocity by the 1st and 12th days did not revealed significant differences.

Figure 2 shows that PICP concentration on the 1st of MI has statistically significant positive correlation with the Tei index ($p=0,026$) and mitral annulus velocity ($p=0,049$). On the 12th day, such findings were not established.

Discussion

The practitioners often contact with HF patients. Previously, this syndrome was considered as a consequence of impaired LV contractility. However, for several decades, systolic and diastolic dysfunctions are considered interconnected links of one global process — pathological cardiac remodeling [11]. In this study, we did not obtain the expected significant relationships between standard parameters revealing LVDD. However, we found relationship between other echocardiographic parameters (Tei index and mitral annulus velocity) and serum PICP levels [12].

There is much literature data that confirm the association of Tei index with HF class, increased in-hospital risk of sudden death, acute HF, arrhythmias, and early post-infarction angina. Tei index can be used to assess LV systolic function [12]. It is also significant for assessing the severity of LVDD. The estimation of the Tei index was proposed by Chuwa Tei in 1995 as a noninvasive Doppler-derived myocardial performance index. The limitation of this method is the technical difficulty of the simultaneous correct visualization. In addition to the technical difficulty, obtained results are affected by parameters such as heart rate and cardiac output. All of the above aspects significantly limit the practical application of this technique [13].

It should be noted that since the introduction of this parameter into clinical practice, studies have proved its more significant value for predicting long-term cardiovascular mortality after MI com-

Table 2

Comparison of echocardiographic parameters during hospitalization

Parameter	1st day of hospitalization Me [$Q_{25;}$ Q_{75}]	12th day of hospitalization Me [$Q_{25;}$ Q_{75}]	p
Left ventricular ejection fraction, %	59,0 [54,0; 63]	62,0 [56,0; 65,0]	<0,0001
End diastolic dimension (cm)	5,35 [5,1; 5,6]	5,4 [5,1; 5,6]	0,9463
End systolic dimension (cm)	3,7 [3,5; 3,9]	3,6 [3,4; 3,9]	<0,0001
End diastolic volume (ml)	135,0 [124,0; 154,0]	135,0 [124,0; 154,0]	0,8190
End systolic volume (ml)	58,0 [51,0; 66,0]	54,0 [47,0; 66,0]	<0,0001
Left atrium (cm)	4,0 [3,9; 4,2]	4,0 [3,9; 4,3]	0,8128
Right atrium (cm)	4,1 [3,9; 4,4]	4,2 [4,0; 4,4]	0,3491
Right ventricle (cm)	1,8 [1,8; 1,8]	1,8 [1,8; 1,8]	0,4226
Interventricular septum (cm)	1,1 [1,0; 1,2]	1,1 [1,0; 1,2]	0,1614
Left ventricular posterior wall (cm)	1,1 [1,0; 1,2]	1,1 [1,0; 1,2]	0,1614
Aorta (cm)	3,5 [3,3; 3,6]	3,5 [3,4; 3,6]	0,0806
End diastolic index (ml/m^2)	68,0 [64,0; 79,0]	70,0 [65,0; 81,5]	0,7794
End systolic index (ml/m^2)	31,0 [25,0; 38,0]	27,5 [23,5; 34,0]	0,1000
Stroke volume (ml)	80,0 [73,0; 90,0]	84,0 [77,0; 92,0]	<0,0001
Myocardial mass (g)	234,0 [206,0; 264,0]	233,0 [206,0; 264,0]	0,2488
Myocardial mass index (g/m^2)	130,0 [102,0; 142,0]	125,0 [111,0; 140,0]	0,2048

Table 3

Comparison of mitral flow parameters assessed by Doppler echocardiography during hospitalization

Parameter	1st day of hospitalization	12th day of hospitalization	p
E (cm/s)	57,0 [50,0; 70,0]	60,0 [49,0; 73,0]	0,6784
A (cm/s)	70,0 [60,0; 79,0]	70,0 [58,0; 80,0]	0,6051
E/A	0,80 [0,71; 1,22]	0,79 [0,68; 1,21]	0,9869
IVRT (ms)	111,0 [104,0; 118,0]	106,0 [104,0; 118,0]	0,1298
IVRT (ms)	107,0 [104,0; 118,0]	106,0 [104,0; 118,0]	0,2310
DT(ms)	196,0 [170,0; 224,0]	189,5 [170,0; 222,0]	0,0494
AT (ms)	124,0 [111,0; 141,0]	131,0 [111,0; 137,0]	0,4603
ET (ms)	294,0 [280,0; 313]	287,0 [268,0; 303,0]	0,1386
dE (ms)	242,0 [222,0; 274,0]	238,0 [204,0; 272,5]	0,0124
dA (ms)	157,0 [132,0; 176,0]	157,0 [132,0; 176,0]	0,5720
IVCT (ms)	91,0 [85,0; 98,0]	90,0 [83,0; 97,0]	0,0128
Diastolic stiffness	0,073 [0,060; 0,085]	0,071 [0,060; 0,080]	0,0533
Em	7,0 [6,0; 8,0]	6,0 [5,0; 8,0]	0,0290
Am	8,0 [6,9; 9,0]	8,0 [7,0; 9,0]	0,2578
Em/Am	0,83 [0,71; 1,17]	0,75 [0,67; 1,12]	0,0003
E/Em	8,8 [7,6; 11,4]	9,0 [7,5; 10,43]	0,0838
Early mitral flow propagation velocity (sm/s)	41,0 [34,0; 48,0]	42,0 [35,0; 51,0]	0,0000
Em/early mitral flow propagation velocity	1,5 [1,13; 2,0]	1,3 [0,98; 1,84]	0,0015
Tei index	0,70 [0,64; 0,75]	0,69 [0,65; 0,78]	0,552
Mitral annulus velocity	7 [6; 8]	7 [6; 8]	0,944

pared with the E/A ratio and the LV wall motion score index. However, there is a little information about the relationship of serum fibrosis markers and echocardiographic parameters of DD. Of particular interest in such combinations is due to the steady increase in the number of patients with HF with preserved ejection fraction (HFpEF) [7]. The aim of such studies is to search for a significant marker for determining individual strategy of management and timely therapy change in patients with risk of HF progression, despite the preserved LV contractility [14].

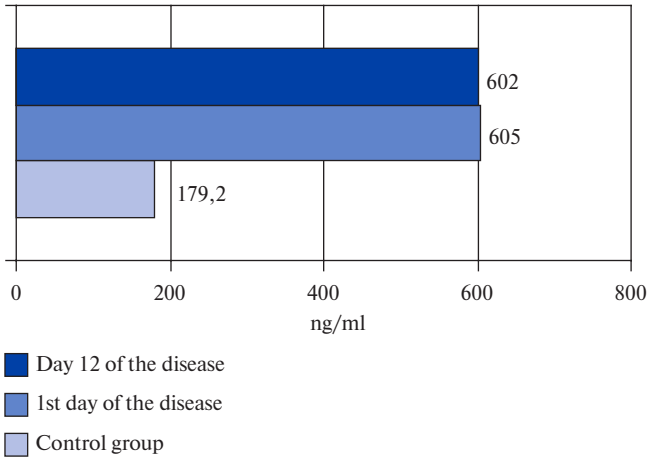

Figure 1. The changes of PICP in comparison with the control group during hospitalization.

The practical introduction of tissue Doppler imaging made it possible to evaluate the systolic velocity and amplitude of atrioventricular annular motion. One of the informative methods for analyzing LV myocardial function is assessing of mitral annular motion, most often — its lateral edge. According to the literature data, there are differences in the normative values of velocity parameters. Nevertheless, some studies have shown that tissue Doppler imaging of the mitral annulus provides the most detailed and accurate picture of the LV diastolic function than the standard parameters of mitral flow. It was established that with E-wave decrease and A-wave increase, DD deteriorates. The relationship of these parameters with the LVEF has been proven. The study by Naumenko EP, et al. (2014) revealed that peak systolic mitral annulus velocity (S') in patients with HFpEF is higher than in patients with systolic dysfunction, but less than in individuals without HF. This indicates subclinical systolic dysfunction. The peak S' $\geqslant$10 cm/s, estimated by spectral tissue Doppler imaging, make it possible to distinguish satisfactory LV contractility from reduced. The combination of E' decrease <8,5 cm/s and the E/A ratio <1,0 indicates pseudonormal mitral flow (sensitivity — 88%, specificity — 67%).

The present study revealed significant correlation of mitral annulus velocity and Tei index with PICP concentration on the 1st day of MI. It was proved that PICP, a type I collagen precursor, is characterized by large diameter fibers and numerous cross-links. It is

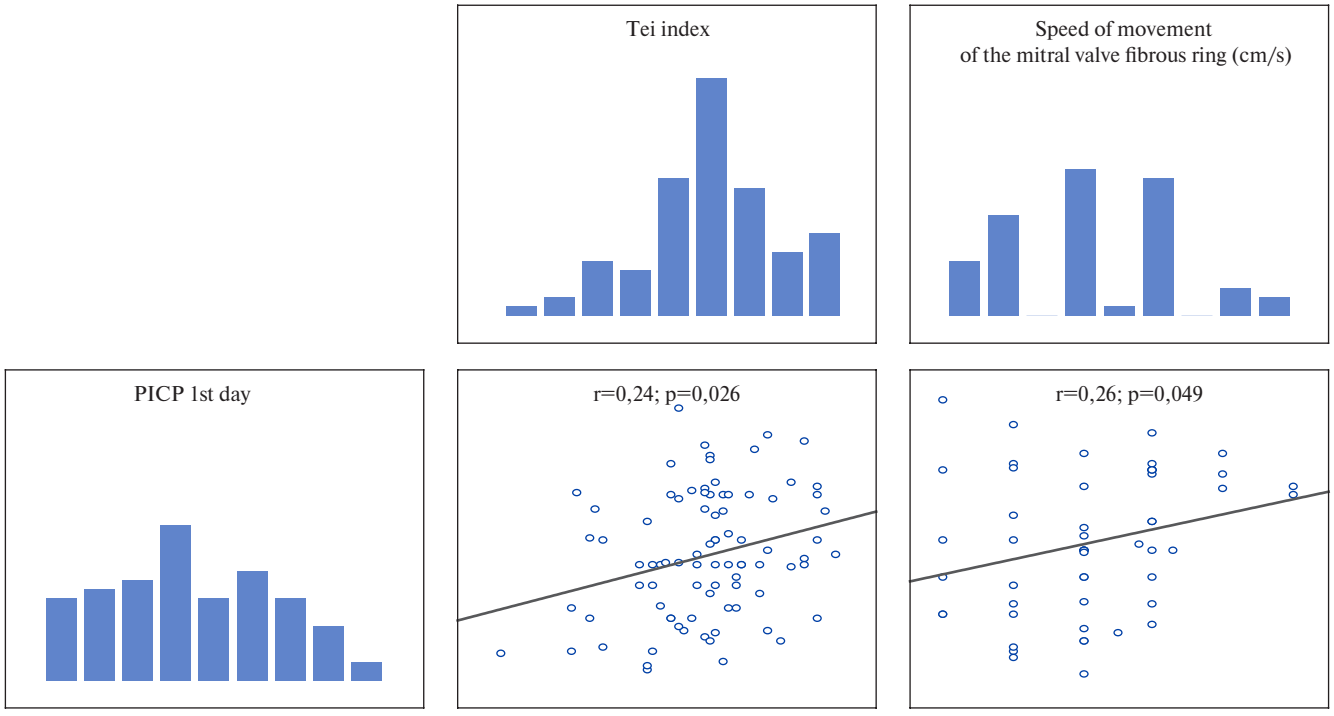

Figure 2. Correlation between PICP and echocardiographic parameters.

PICP that is associated with diffuse myocardial fibrosis, which is characterized by most unfavorable prognosis in HF patients [15].

Assessment of echocardiographic parameters during hospitalization revealed LVEF decrease <50% in 13 patients. We observed an increase in the number of ultrasound parameters with values indicating the LVDD deterioration. It is important that there were no clinical manifestations of HF aggravation during hospitalization. Perhaps these negative changes are the initial manifestation of impaired myocardial relaxation. It is at this stage that is important to identify patients who have a potential risk of HFpEF.

Study limitation: the analysis of peripheral serum biomarkers does not have 100% specificity and is inferior to the morphological diagnosis of fibrosis, namely the determination of the collagen volume fraction (biopsy).

Conclusion

During hospitalization of patients with STEMI and preserved LVEF, an increase in the proportion of subjects with DD and some impairment of systolic function were found. Positive correlation was established between the concentration of PICP with mitral annulus velocity and the Tei index, indicating an association between myocardial fibrosis and DD.

Relationships and Activities: not.

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Mechanisms and predictors of ischemic mitral regurgitation at rest and on exertion in patients at early stage of myocardial infarction

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Aim. Determination of the mechanisms and predictors of ischemic mitral regurgitation (IMR) at rest and on exertion in patients at early stage of myocardial infarction (MI).

Material and methods. Seventy-seven patients with inferoposterior MI and 79 patients with anteroseptal apical MI were examined on the 7th day at rest and after exertion. We determined the degree of IMR (according to the PISA method), posteromedial and anterolateral papillary muscle (PM) displacement, closure height of the mitral valve (MV), systolic and diastolic mitral valve orifice area, volume of the left ventricle (LV), LV contractility index, deformation of the infarction regions, general LV deformation, deformation and systolic dyssinchrony of the PM.

Results. IMR was more common in inferior MI (42% vs 28%). LV volumes in cases with anteroseptal apical MI and IMR were greater and LV deformation was less than in patients without IMR. In inferoposterior MI and IMR, differences were observed in the index of local contractility and function of the posteromedial PM. The differences in MI of both localizations and IMR compared with MI without IMR were the areas of the mitral orifice and dyssinchrony of the PM. The degree of IMR after exertion did not depend on the degree of IMR at rest. Predictors of IMR at rest in MI of both localizations were the apical displacement of MV closure and the area of the mitral orifice. In inferoposterior, posteromedial PM displacement, deformation of the infarcted areas, PM dyssinchrony were also predictors. In anteroseptal apical MI, the area of the mitral orifice was the predictor of IMR. Predictors of anteroseptal apical MI after physical exertion after inferior MI were mitral orifice areas, contractility index, displacement and deformation of the posteromedial PM. In anteroseptal apical MI, the IMR predictors were MV closure height and systolic area of mitral orifice.

Conclusion. The study confirms the significance of changing the spatial orientation of the MV structures in MI of both localizations, impaired regional contractility in inferoposterior MI and LV volume in anteroseptal apical MI at early stage of the disease.

Key words: ischemic mitral regurgitation; longitudinal deformation; papillary muscle dyssinchrony.

Relationships and Activities: not.

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Ischemic mitral regurgitation (IMR) is a complication of myocardial infarction (MI) and an independent predictor of morbidity and mortality [1, 2]. IMR develops in patients with normal mitral valve (MV) leaflets as a result of left ventricular (LV) dysfunction and remodeling, mitral annulus dilatation, and papillary muscle (PM) displacement [2, 3]. These processes depend both on the MI size and localization [4]. IMR is the result of a change in the geometric relationship of the LV and the MV apparatus, and it can change both in time and depending on the state of rest or physical activity [5].

The aim was to study the mechanisms of IMR and its changes at rest and during exertion in the early stage of MI with various localization.

Material and methods

The study included 77 patients with primary inferior-posterior myocardial infarction and 79 patients with acute anteroseptal-apical myocardial infarction aged 57±5 years, who were hospitalized within 12 hours from the MI onset.

The control group consisted of 50 healthy individuals of the same age, gender and weight.

There were following exclusion criteria: history of mitral insufficiency, structural changes of MV, aortic valve disease, arrhythmia, diabetes and kidney failure.

Patients underwent stenting of culprit artery.

Patients with MI of each localization were divided into two subgroups depending on the severity of mitral regurgitation: grade 0-I or grade I-IV.

Left ventricular ejection fraction (LVEF), left atrial systolic volume index, left ventricular mass index (LVMI), and LV global and regional contractility indices were calculated according to the American Society of Echocardiography guidelines using GE Vivid 7 ultrasound system [6].

The LV sphericity index was calculated as the ratio of LV end-systolic volume (x 100%) to hypothetical sphere volume (4/3) π(d/2)3, where 'd' is the diameter of LV long axis.

The MV coaptation height was assessed at end-diastole in a 3-chamber view. The surface area of apical mitral leaflet displacement, formed by the mitral annulus and leaflets, was measured at middle systole in a 3-chamber position.

Apical displacement of PM was measured for anterolateral and posteromedial PM, respectively (Figure 1, 2). The posterior and lateral displacement of PM was measured in the parasternal long axis view at the PM level [7].

Mitral valve orifice area (MVOA) at the systole and diastole was calculated using the ellipse equation π*r1*r2/4, where 'r1' and 'r2' are the anteroposterior and intercomissary diameters of the MV, respectively. The mitral annular fractional shortening was calculated by the equation 100% x (diastolic MVOA — systolic MVOA)/diastolic MVOA.

The grade of mitral regurgitation (MR) was assessed by the PISA method [8] with the determination of regurgitant orifice area (ROA) and regurgitant volume (RV). There were following grades of MR: I — RV <20 ml or ROA <0,20 cm^2; II — RV= 20-39 ml or ROA =0,20-0,29 cm^2; III — RV =40-59 ml or ROA =0,30-0,39 cm^2; IV — RV >60 ml or ROA >0,40 cm^2. The change in the IMR grade was determined by the ROA change ⩾0,1 cm^2.

The PM function was studied using the speckle tracking echocardiography in 4- and 3-chamber views to determine the longitudinal strain of both PM (Figure 3) [9]. The strain peaks and the time from QRS onset to the strain peak of both PM were measured. The difference of this value specifies the PM dissynchrony [10].

Segment and global LV strain were measured by particle tracking method (Figure 4). The strain of LV infarcted walls was determined as the ratio of the sum of the infarcted walls' segment strain and the number of analyzed segments.

Treadmill stress echocardiography was performed until symptom onset or heart rate reached 120 bpm. Images obtained during the first minute of rest. Contractility improvement was evaluated by increasing the contractility index ⩾1.

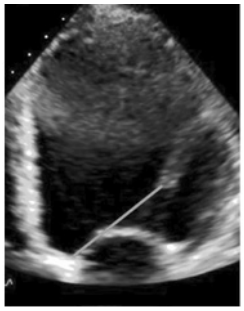

Figure 1. Determination of the apical displacement of anterior PM.

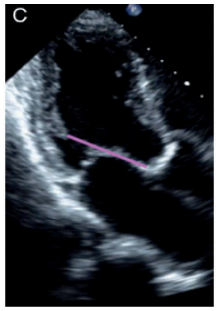

Figure 2. Determination of the apical displacement of posteromedial PM.

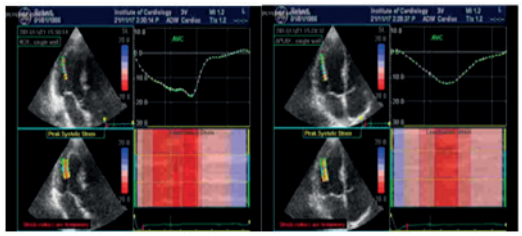

Figure 3. Measurement of PM strain and dyssynchrony.

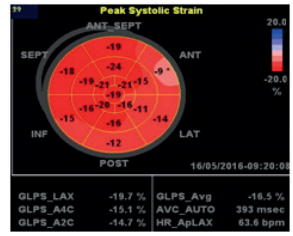

Figure 4. Determination of strain of LV and infarcted segments.

Statistical analysis was performed using the software package SPSS 21.0. Values are presented as m±SD. Continuous parameters were evaluated by Student's t-test and Mann-Whitney U-test. Differences were considered significant at $p<0,05$.

Variables were studied to determine the normal distribution and equal deviations using the Kolmogorov-Smirnov test.

Correlation analysis was performed to assess linear dependencies. Correlation between parameters were considered reliable at $R \geqslant 0,4$.

Binary regression analysis was used to identify independent predictors of IMR.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committees of all participating centers approved this study. All patients signed informed consent.

Results

The number of patients with inferior-posterior MI and IMR at rest was significantly higher than patients with anteroseptal apical MI and IMR. The data are shown in Table 1. In patients with MI of the same localization, the parameters differed depend-

Table 1

Clinical characteristics of patients with inferior-posterior and anteroseptal apical MI and IMR at rest

Parameters	Inferior-posterior MI	Anteroseptal apical MI	Control	P		
	A	B	C	A vs B	A vs C	B vs C
Demographic and clinical data						
Number of patients (n/%)	32/42	22/28	50	0,03	<0,001	<0,001
Age (years)	54±5	54±5	54±5	НД	НД	НД
Gender, women (%)	43,2	38,3	34,6	НД	НД	НД
BMI, kg/m^2	26,4±3,2	25,9±3,0	25,5±3,1	НД	НД	НД
Hypertension (%)	56,7	57,1	0	НД	НД	<0,001
Dyslipidemia (%)	72	76	32	НД	НД	<0,001
Drugs						
Beta blockers (%)	94	95	0	НД	НД	<0,001
ACE inhibitors (%)	92	97	0	НД	НД	<0,001
Statins (%)	83	85	0	НД	НД	<0,001
Spironolactone (%)	39	41	0	НД	НД	<0,001
Standard echocardiography						
ESVI (ml/m^2)	27,5±9,1	36,4±10,2	21,3±5,9	0,02	НД	0,01
EDVI (ml/m^2)	52,4±9,8	63,7±11,3	52,3±9,8	0,02	НД	0,01
SI (%)	16±5	16±9	15±7	НД	НД	НД
EF (%)	52,3±6,2	45,4±4,1	58,7±4,3	0,01	0,03	0,01
LVMI (g/m^2)	110±19,8	114±21,4	73,6±18,4	НД	0,04	0,04
LAVI (ml/m^2)	29,5±5,1	29,2±5,3	27,8±4,7	НД	НД	НД

Contractility (RCI, GCI)						
Inferior wall	5,8±1,5	4,3±1,1	3,0±0,0			
Inferior-septal wall	5,9±1,4	3,0±0,0	3,0±0,0	0,008	0,008	НД
Posterior wall	5,7±1,6	3,0±0,0	3,0±0,0	0,009	0,009	НД
Lateral wall	3,1±0,3	3,2±0,6	3,0±0,0	НД	НД	НД
Anterior wall	3,0±0,0	7,3±1,8	3,0±0,0	0,003	НД	0,003
Anterior-septal wall	3,0±0,0	6,9±1,9	3,0±0,0	0,004	НД	0,004
GCI	1,4±0,3	1,6±038	1,0±0,0	0,02		0,002
Echocardiography of mitral valve apparatus						
MV coaptation height (cm)	0,97±0,23	0,98±0,21	0,86±0,19	НД	0,03	0,03
Systolic mitral valve prolapse area (mm^2)	163,4±63,4	166,3±68,2	121,6±37,4	НД	0,01	0,01
Systolic MVOA (mm^2)	564,6±114,2	486,7±117,6	342,6±114,2	0,01	НД	НД
Diastolic MVOA (mm^2)	715,4±128,3	681,2±119,4	594,6±117,2	0,01	НД	НД
MAFS (%)	18±3	24±5	35±7	0,02	0,008	НД
Apical displacement of ALPM (cm)	3,28±0,86	3,64±0,97	3,12±0,81	НД	НД	НД
Apical displacement of PMPM (cm)	3,79±0,91	3,37±0,90	3,21±0,78	НД	НД	НД
PMPMpost (mm)	4,5±1,9	3,1±1,8	2,4±1,3	0,02	0,01	НД
PMPMlat (mm)	2,6±1,5	2,2±1,1	1,9±1,1	0,04	0,02	НД
ALPMpost (mm)	2,4±1,2	2,6±1,5	2,1±1,2	НД	НД	НД
ALPMlat (mm)	2,3±1,4	2,5±1,4	2,0±1,0	НД	НД	НД
Speckle tracking echocardiography						
LVLS (%)	-16,8±1,9	-14,6±1,8	-20,3±2,1	0,04	НД	0,01
ISLS (%)	-9,2±6	-9,7±3	—	НД	—	—
LS ALPM (%)	-13,9±1,2	-13,9±1,1	-15,8±1,7	НД	0,03	0,03
LS PMPM (%)	-13,8±1,3	-15,1±1,2	-15,6±1,7	0,02	0,01	НД
PMSD (ms)	38±11	42±14	16±9	НД	0,02	0,01

Abbreviations: ALPM — antero-lateral papillary muscle, ALPMlat/post — direction of anterolateral papillary muscle displacement, EDVI — end-diastolic volume index, EF — ejection fraction, ESVI — end-systolic volume index, GCI — global contractility index, IMR — ischemic mitral regurgitation, ISLS — longitudinal strain of infarcted segments, LAVI — left atrial volume index, LS — longitudinal strain, LVLS — left ventricular longitudinal strain, LVMI — left ventricular mass index, MAFS — mitral annular fractional shortening, MV — mitral valve, MVOA — mitral valve orifice area, PMPM — posteromedial papillary muscle, PMSD — papillary muscle systolic dyssynchrony, PMPMlat/post — direction of posteromedial papillary muscle displacement, RCI — regional contractility index, SI — sphericity index.

Table 2

Parameters with significant differences in patients with anteroseptal apical MI depending on the presence of IMR at rest

Parameters	No IMR (A)	IMR (B)	Control (C)	P		
				A vs B	A vs B	A vs B
ESVI (ml/m^2)	32,8±8,4	36,4±10,2	21,3±5,9	<0,03	<0,01	<0,01
EDVI (ml/m^2)	57,8±10,3	63,7±11,3	52,3±9,8	<0,02	<0,01	<0,01
Systolic MVOA (mm^2)	418,4±113,6	486,7±117,6	342,6±114,2	<0,05	<0,05	<0,02
Diastolic MVOA (mm^2)	656,3±121,3	681,2±119,4	594,6±117,2	<0,05	<0,05	<0,02
MAFS (%)	29±7	24±5	35±7	<0,05	<0,05	<0,01
LVLS (%)	-15,2±1,5	-14,6±1,8	-20,3±2,1	<0,03	<0,05	<0,01
PMSD (ms)	23±10	42±14	16±9	<0,01	<0,05	<0,01

Abbreviations: EDVI — end-diastolic volume index, ESVI — end-systolic volume index, IMR — ischemic mitral regurgitation, LVLS — left ventricular longitudinal strain, MAFS — mitral annular fractional shortening, MVOA — mitral valve orifice area, PMSD — papillary muscle systolic dyssynchrony.

Table 3

Parameters with significant differences in patients with inferior-posterior MI depending on the presence of IMR at rest

Параметры	No IMR (A)	IMR (B)	Control (C)	A vs B	A vs B	A vs B
Systolic MVOA (mm^2)	467,3±117,8	564,6±114,2	342,6±114,2	<0,02	<0,03	<0,01
Diastolic MVOA (mm^2)	697,2±124,2	715,4±128,3	594,6±117,2	<0,02	<0,03	<0,01
MAFS (%)	28±5	18±3	35±7	<0,01	<0,02	<0,003
PMSD (ms)	21±7	38±11	16±9	<0,001	<0,001	<0,001
RCI (inferior wall)	5,2±1,3	5,8±1,5	3,0±0,0	<0,05	<0,02	<0,01
RCI (inferior-septal wall)	4,6±1,1	5,9±1,4	3,0±0,0	<0,05	<0,02	<0,01
RCI (posterior wall)	4,8±1,2	5,7±1,6	3,0±0,0	<0,05	<0,03	<0,01
Apical displacement of PMPM (cm)	3,35±0,86	3,79±0,91	3,21±0,78	<0,03	НД	<0,03
PMPMpost (mm)	3,2±0,9	4,5±1,9	2,4±1,3	<0,02	<0,02	<0,01
PMPMlat (mm)	2,1±1,2	2,6±1,5	1,9±1,1	<0,05	<0,03	0,02
ISLS (%)	-12,7±4	-9,2±6	—	<0,03	—	—
LS PMPM (%)	-11,3±1,4	-13,8±1,3	-15,6±1,7	<0,02	<0,01	<0,02

Abbreviations: IMR — ischemic mitral regurgitation, ISLS — longitudinal strain of infarcted segments, MAFS — mitral annular fractional shortening, MVOA — mitral valve orifice area, LS — longitudinal strain, PMPM — posteromedial papillary muscle, PMPMlat/post — direction of posteromedial papillary muscle displacement, PMSD — papillary muscle systolic dyssynchrony, RCI — regional contractility index.

Table 4

ROA change after exertion in patients with inferior-posterior MI

Parameters	ROA change after exertion		P	Correlation with ROA	
	Decrease, n=12 (37,5%)	Increase, n=20 (62,5%)		R	P
Heart rate (bpm)	32±15	35±14	НД	0,11	0,61
SBP (mm Hg)	28±15	29±10	НД	0,19	0,34
ESV (ml)	-12±11	-13±12	НД	0,12	0,27
EDV (ml)	-5,3±11	0,8±19	НД	0,14	0,35
SI (%)	-3±4	-1±3	НД	0,12	0,39
EF (%)	7,3±6,4	7,9±6,8	НД	0,21	0,18
LAV (ml)	-1,3±2,3	-1,4±2,1	0,06	0,42	0,08
MV coaptation height (cm)	-0,21±0,18	0,07±0,11	<0,002	0,65	0,01
Systolic mitral valve prolapse area (mm^2)	-1,2±1,9	0,6±2,1	<0,002	0,74	<0,002
Systolic MVOA (mm^2)	-51,3±72,4	62,2±52,1	0,01	0,52	0,02
Diastolic MVOA (mm^2)	-42,4±68,3	51,6±48,3	0,01	0,48	0,02
MAFS (%)	2,3±11,4	-1,2±9,7	0,03	0,46	0,03
Apical displacement of ALPM (cm)	-3,4±2,1	-3,2±1,9	НД	0,31	0,17
Apical displacement of PMPM (cm)	-2,0±1,7	0,6±2,1	<0,03	0,57	<0,03
PMPMpost (mm)	-2,5±1,7	1,1±1,5	<0,002	0,67	<0,005
PMPMlat (mm)	-1,7±1,7	-0,5±1,5	<0,005	0,51	<0,005
ALPMpost (mm)	-2,1±1,5	0,7±1,6	<0,002	0,60	<0,002
ALPMlat (mm)	-1,3±1,0	0,9±1,1	НД	0,34	0,07
RCI (inferior wall)	-0,7±0,15	-0,3±0,12	<0,002	0,68	<0,002
RCI (inferior-septal wall)	-0,6±0,13	-0,2±0,14	<0,002	0,65	<0,002
RCI (posterior wall)	-0,5±0,12	-0,3±0,11	<0,05	0,47	<0,05
RCI (lateral wall)	-0,2±0,18	-0,1±0,11	НД	0,31	0.09
GCI	-0,6±0,14	-0,24±0,13	<0,002	0,64	<0,002

LS ALPM (%)	-1,3±0,7	-1,4±0,7	НД	0,28	0,12
ISLS (%)	3,7±5	-1,8±4	<0,003	0,68	0,004
LS PMPM (%)	-1,9±1,2	1,8±1,2	<0,001	0,78	<0,001
LVLS (%)	1,1±1,3	-0,8±1,8	НД	0,38	<0,07
PMSD (ms)	2,1±1,5	6,9±3,2	<0,01	0,53	<0,01

Abbreviations: ALPM — antero-lateral papillary muscle, ALPMlat/post — direction of anterolateral papillary muscle displacement, EDVI — end-diastolic volume index, EF — ejection fraction, ESV — end-systolic volume, EDV — end-diastolic volume, GCI — global contractility index, IMR — ischemic mitral regurgitation, ISLS — longitudinal strain of infarcted segments, LAV — left atrial volume, LAVI — left atrial volume index, LS — longitudinal strain, LVLS — left ventricular longitudinal strain, LVMI — left ventricular mass index, MAFS — mitral annular fractional shortening, MV — mitral valve, MVOA — mitral valve orifice area, PMPM — posteromedial papillary muscle, PMSD — papillary muscle systolic dyssynchrony, PMPMlat/post — direction of posteromedial papillary muscle displacement, RCI — regional contractility index, SBP — systolic blood pressure, SI — sphericity index.

Table 5

ROA change during exercise in patients with anteroseptal apical MI

Parameters	ROA change after exertion		P	Correlation with ROA	
	Decrease, n=10 (45,5%)	Increase, n=12 (54,5%)		R	P
Heart rate (bpm)	34±12	36±15	НД	0,14	0,68
SBP (mm Hg)	30±17	28±14	НД	0,21	0,42
ESV (ml)	-14±9	-12±8	НД	0,18	0,24
EDV (ml)	-5,7±10	1,1±17	НД	0,24	0,28
SI (%)	-4±4	-2±4	НД	0,27	0,21
EF (%)	6,5±6,1	7,4±6,3	НД	0,31	0,11
LAV (ml)	-1,2±2,4	1,1±2,0	0,07	0,39	0,09
MV coaptation height (cm)	-0,24±0,14	0,13±0,14	<0,002	0,64	0,002
Systolic mitral valve prolapse area (mm^2)	-1,3±2,1	0,8±2,0	<0,002	0,74	<0,001
Systolic MVOA (mm^2)	-46,3±68,7	31,6±53,1	0,04	0,47	0,03
Diastolic MVOA (mm^2)	-38,1±39,4	37,4±42,6	0,03	0,43	0,04
MAFS (%)	1,1±9,3	-0,9±8,2	0,04	0,42	0,04
Apical displacement of ALPM (cm)	-3,1±1,9	1,2±1,7	<0,003	0,58	0,002
Apical displacement of PMPM (cm)	-2,2±2,1	-0,6±1,2	<0,05	0,51	<0,05
PMPMpost (mm)	-1,5±1,2	1,4±1,6	<0,004	0,63	0,03
PMPMlat (mm)	-1,9±1,7	-1,5±1,2	НД	0,29	0,23
ALPMpost (mm)	-1,7±1,3	0,9±1,4	<0,002	0,63	0,03
ALPMlat(mm)	-1,4±1,1	0,9±1,1	НД	0,54	0,06
RCI (lateral wall)	-0,1±0,19	-0,2±0,13	НД	0,31	0,09
RCI (anterior wall)	-0,5±0,11	-0,3±0,10	НД	0,23	0,08
RCI (anterior-septal wall)	-0,4±0,16	-0,2±0,15	НД	0,34	0,09
GCI	-0,28±0,12	-0,21±0,15	НД	0,21	0,18
LS ALPM (%)	-1,3±0,7	-1,4±0,7	НД	0,28	0,09
LS PMPM (%)	-2,2±1,1	-1,9±1,3	НД	0,22	0,14
ISLS (%)	1,3±0,9	0,7±0,8	НД	0,32	0,09
LVLS (%)	6,8±1,7	1,3±1,4	<0,003	0,65	<0,002
PMSD (ms)	2,3±1,3	2,5±1,6	НД	0,21	0,14

Abbreviations: ALPM — antero-lateral papillary muscle, ALPMlat/post — direction of anterolateral papillary muscle displacement, EDVI — end-diastolic volume index, EF — ejection fraction, ESV — end-systolic volume, EDV — end-diastolic volume, ESVI — end-systolic volume index, GCI — global contractility index, IMR — ischemic mitral regurgitation, ISLS — longitudinal strain of infarcted segments, LAV — left atrial volume, LAVI — left atrial volume index, LS — longitudinal strain, LVLS — left ventricular longitudinal strain, MAFS — mitral annular fractional shortening, MV — mitral valve, MVOA — mitral valve orifice area, PMPM — posteromedial papillary muscle, PMSD — papillary muscle systolic dyssynchrony, PMPMlat/post — direction of posteromedial papillary muscle displacement, RCI — regional contractility index, SBP — systolic blood pressure, SI — sphericity index.

Table 6

Predictors of IMR (ROA) at rest on the 7th day of MI

Parameters	Inferior-posterior MI	Anteroseptal apical MI
MV coaptation height	0,03	0,01
Systolic mitral valve prolapse area	0,01	0,02
Systolic MVOA	0,01	0,04
Diastolic MVOA	0,03	0,03
MAFS	0,04	0,04
Apical displacement of PMPM	0,001	0,09
ISLS	0,001	0,12
PMSD	0,01	0,05
EDVI	0,23	0.002
ESVI	0,31	0.01
R^2	0,68	0,65

Abbreviations: EDVI — end-diastolic volume index, ESVI — end-systolic volume index, IMR — ischemic mitral regurgitation, ISLS — longitudinal strain of infarcted segments, MAFS — mitral annular fractional shortening, MV — mitral valve, MVOA — mitral valve orifice area, PMPM — posteromedial papillary muscle, PMSD — papillary muscle systolic dyssynchrony.

Table 7

Предикторы ИМР (ПРО) после нагрузки

Parameters	Inferior-posterior MI	Anteroseptal apical MI
MV coaptation height	0,005	0,001
Systolic mitral valve prolapse area	0,0001	0,002
Systolic MVOA	0,001	0,01
PMPMpost	0,0001	0,04
Apical displacement of PMPM	0,02	0,07
LS PMPM	0,0001	0,09
ISLS	0,004	0,08
R^2	0,73	0,71

Abbreviations: IMR — ischemic mitral regurgitation, ISLS — longitudinal strain of infarcted segments, MV — mitral valve, MVOA — mitral valve orifice area, PMPM — posteromedial papillary muscle, PMPMlat/post — direction of posteromedial papillary muscle displacement.

ing on the presence of IMR (Tables 2, 3). Changes of IMR grade after exertion in patients with MI of both localizations did not depend on the IMR grade at rest. These changes after exertion are shown in Tables 4, 5.

Predictors of IMR at rest and after exertion differed in patients with MI of both locations (Tables 6, 7).

Discussion

The study is devoted to identifying the mechanisms of early IMR at rest and during exercise in patients with MI of various localization. Studies of IMR both in the early period of MI, and depending on the MI localization, are few. The prevalence of IMR in patients with MI is 50%; 38% is characterized by moderate severity, and 12% — moderate-severe and severe [2]. IMR is diagnosed between 7 and 30 days after onset of MI [4].

We performed the study on the 7th day of MI for early detection of changes that contribute to IMR development. According to our data, IMR is present in the early stages of MI and more often in patients with inferior-posterior MI. To study LV contractility and PM function, the speckle tracking echocardiography with strain assessment was used. According to the study, the deformation of infarcted segments was a predictor of IMR for inferior-posterior MI, and the PM dyssynchrony — IMR predictor for MI of both localizations. Little research has been done on PM strain and dyssynchrony [9, 10], and there are no studies on the early period of MI. According to our data, PM dyssynchrony >30 ms is a predictor of IMR.

The aim of the study was also to determine the mechanisms and predictors of IMR during exertion.

The contractility change during exertion alters the impact on the MV coaptation. During exertion, changes in LV geometry can alter the orientation of the MV structures and IMR severity. On the other hand, Increased contractility of PM can aggravate MV leaflets displacement and exacerbate the IMR. IMR at rest depends on ROA, the systolic pressure gradient, and the duration of systole [5]. During exercise, the systolic pressure gradient increases, the systole duration decreases, and the RV becomes dependent mainly on the ROA.

According to our data, the IMR severity during exertion in patients with MI does not depend on the IMR severity at rest.

In patients of both subgroups, with a IMR severity change, the same increase in heart rate and systolic blood pressure was observed. Thus, systolic shortening does not affect the IMR severity. The initial LV sizes, which play a role in the IMR onset at rest in anteroseptal apical MI, did not affect the IMR severity and were not predictors of IMR changes during exertion.

In fact, IMR severity change during exertion does not depend on the LV size and function, but depends on the MV geometry.

Indeed, MV coaptation height and the systolic area under MV leaflets during exertion correlated with the ROA and were predictors of IMR severity. The systolic mitral valve orifice area was a predictor of IMR severity changes in during exertion in patients with MI of both localizations.

An aggravation in the apical displacement of anterior PM during exertion was associated with an IMR severity increase in patients with anteroseptal apical MI and correlated with the ROA. However, this parameter did not affect the IMR severity at rest in these patients.

The direction of the regurgitant jet was different in patients of both groups. Patients with inferior-posterior MI had eccentric regurgitation; in patients with anteroseptal apical MI, the jet direction was more central. In these patients, the apical displacement of both PM leads to a more symmetrical displacement, which provides a central direction of IMR. Contractility impairment of LV segments in patients with inferior-posterior MI can lead to a greater displacement of the posteromedial PM, providing asymmetric displacement of MV leaflets and eccentric IMR.

IMR severity decrease during exertion was more often observed in patients with inferior-posterior MI due to improved contractility of the infarcted zone, which led to MVOA decrease, an improvement of the mitral annular function, and orientation of the posteromedial PM.

In patients with inferior-posterior MI, posteromedial PM strain augment during exertion increased the IMR severity due to the greater posterior displacement of MV leaflets. In patients with anteroseptal apical MI, a change in the strain of both PM did not affect the IMR severity during exertion, and a change in LV deformation led to alteration in IMR severity.

Thus, in patients with MI of early stage, IMR is dynamic in nature, and its intensity varies at rest and during exercise. The parameters that correlate with the presence and severity of IMR at rest and during exertion, like the IMR predictors, are different.

Relationships and Activities: not.

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