Cardiovascular Therapy and Prevention. 2021;20(1):2494.
doi:10.15829/1728-8800-2021-2494
ISSN 1728-8800 (Print)
ISSN 2619-0125 (Online)

N-terminal propeptide of type III procollagen for predicting diastolic dysfunction in patients with myocardial infarction and preserved ejection fraction

Osokina A.V., Karetnikova V.N., Polikutina O.M., Ivanova A.V., Avramenko O.E., Gruzdeva O.V., Barbarash O.L.

Research Institute for Complex Issues of Cardiovascular Diseases. Kemerovo, Russia

Aim. To study changes in the level of fibrotic scarring marker — the N-terminal propeptide type III procollagen (PIIINP) and structural and functional parameters with the assessment of diastolic function in patients a year after ST segment elevation myocardial infarction (STEMI) and preserved left ventricle (LV) contractility.

Material and methods. At first, the study included 120 (100%) STEMI patients. Next, patients with an LV ejection fraction (EF) ⩾50% were selected. The final analysis included 86 STEMI patients. Upon hospitalization, the patients underwent routine diagnostic tests, coronary angiography with stenting of culprit artery. Echocardiography and determination of venous blood PIIINP and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels was on the 1st (time point 1) and 12th day (time point 2) of disease and after a year (time point 3). To compare the obtained values of fibrotic scarring markers, a control group was formed, including 20 (100%) healthy volunteers, identical in age and sex with the studied sample.

Results. On the first day of MI, 25 (29,1%) patients with signs of diastolic dysfunction (DD) were identified among those with preserved LVEF. After 1 year, the number of such patients increased by 10% (n=9). Initially increased (relative to the control group) concentration of PIIINP on the first day (311,2 [220,1; 376,3] ng/ml) decreased by the 12th day (223,3 [195,3; 312,1] ng/ml) and returned to the initial values a year after the MI (312,6 [228,0; 383,8] ng/ml). The NT-proBNP concentration during the hospitalization period did not exceed the reference values and did not differ between 1 and 2 time points (p=0,127). One year later, the NT-proBNP concentration significantly exceeded the values of the previous determinations and amounted to 124,4 pg/ml (p=0,043). According to the ROC analysis, with a PIIINP ⩾387,8 ng/ml on the first day, the risk of DD increases (p=0,050, sensitivity, 84,62%, specificity, 55,56%) within a year after STEMI with preserved LVEF.

Conclusion. The threshold of PIIINP (⩾387,8 ng/ml) was established for the first day of MI, at which the risk of DD increases one year after the index event. An increase in NT-proBNP concentration one year after STEMI indicates the progression of heart failure.

Keywords: myocardial infarction, diastolic dysfunction, fibrotic scarring markers, heart failure.

Relationships and Activities: none.

Osokina A.V.* ORCID: 0000-0002-7784-5824, Karetnikova V.N. ORCID: 0000-0002-9801-9839, Polikutina O.M. ORCID: 0000-0001-7458-6962, Ivanova A.V. ORCID: 0000-0001-7993-5789, Avramenko O.E. ORCID: 0000-0003-3441-372X, Gruzdeva O.V. ORCID: 0000-0002-7780-829X, Barbarash O.L. ORCID: 0000-0002-4642-3610.

*Corresponding author: osokav@kemcardio.ru, av.osokina80@yandex.ru

Received: 10/03-2020
Revision Received: 25/04-2020
Accepted: 26/05-2020

For citation: Osokina A.V., Karetnikova V.N., Polikutina O.M., Ivanova A.V., Avramenko O.E., Gruzdeva O.V., Barbarash O.L. N-terminal propeptide of type III procollagen for predicting diastolic dysfunction in patients with myocardial infarction and preserved ejection fraction. *Cardiovascular Therapy and Prevention*. 2021;20(1):2494. (In Russ.) doi:10.15829/1728-8800-2021-2494

Introduction

Diastolic dysfunction (DD) of the left ventricle (LV) is currently the subject of scientific interest due to its high frequency among patients with cardiovascular diseases, including coronary artery disease (CAD), and an adverse effect on prognosis. The data on the formation of DD, its early diagnosis and the possibility of therapeutic effects are ambiguous [1]. It has been proven that DD can form independently from impaired contractile function. DD is directly related to impaired exercise tolerance and the patient's quality of life [2]. Systolic dysfunction is formed exclusively together with diastolic dysfunction, which excludes the possibility of an isolated variant [3]. As a rule, the long-term prognosis of patients with DD is disappointing due to a set of clinical factors and echocardiographic (EchoCG) indicators of LV myocardial function. There is an opinion that impaired diastolic function (DF) develops earlier than electrocardiographic signs of ischemia, impaired contractility. DF is one of the early indicators of myocardial ischemia in patients with angina pectoris [4], and fibrosis is one of the key mechanisms for the development and progression of LV myocardial dysfunction. Today, close attention of scientists is focused on the study of seromarkers of myocardial fibrosis and collagen precursors. There is particular scientific interest in markers characterizing the activity of the production and breakdown of collagen. Among others, collagen precursors of type I and type III are being actively studied [5]. The information available

for analysis on the existing connections of fibrotic seromarkers with structural and functional parameters of the heart on echocardiography, including after myocardial infarction (MI) with preserved LV ejection fraction (EF), are ambiguous, which determines the need for a more thorough study of this issue.

The aim is to study changes in the dynamics of biochemical fibrotic marker of the N-terminal propeptide type III procollagen (PIIINP) and structural and functional parameters with the assessment of diastolic function in patients a year after ST segment elevation myocardial infarction (STEMI) and preserved left ventricle (LV) contractility.

Material and methods

The study protocol was approved by the local ethics committee of the Research Institute for Complex Issues of Cardiovascular Diseases. The study included 120 STEMI patients. In 100% of cases, patients had indications for emergency hospitalization. The enrollment was carried out by the method of continuous sampling during 7 months of 2015.

Enrollment criteria:

1) diagnosis of STEMI, established according to the recommendations of the European Society of Cardiology (2015);

2) informed consent to participate in the study, signed by the patient;

3) patient >18 years old;

4) heart failure (HF) according to the Killip classification not >III.

Withdrawal criteria:

1) concomitant pathology, clinically significant at the time of enrollment (oncopathology, chronic diseases in the acute stage, mental illness);

2) acute coronary syndrome (as a complication of percutaneous coronary intervention or coronary artery bypass graft);

3) patients >80 years old;

4) the severity of HF according to the Killip classification — IV;

5) death of the patient on the first day of hospitalization.

The average age in the sample is 57,75 [52,4; 63,6] years. Women accounted for 24,3% (n=29); each of them was postmenopausal. The overwhelming part of the sample is represented by men, n=91 (75,8%). At the time of hospitalization, all the necessary examinations were carried out to verify myocardial infarction, including standard instrumental and laboratory ones. In addition, on admission, coronary angiography with stenting of culprit artery was performed in 100% of cases. EchoCG was performed on the 1st (time point 1), 12th day (time point 2) of disease and a year after myocardial infarction (time point 3) on the device "Aloka α-10 ProSound" in modes M- and B-, pulse-wave, continuous-wave doppler modes, in color flow mapping mode, in tissue doppler ultrasonography mode and color doppler M-mode (Color M-mode) using an ultrasonic matrix sensor 2-4 MHz. The study was performed in standard positions, with the patient on the left side (Clinical guidelines of RHFS-RSC-RSMSP (Russian Heart Failure Society — Russian Society of Cardiology — Russian Scientific Medical Society of Physicians), HF: chronic (CHF) and acute decompensated HF, diagnosis, prevention and treatment, 2018). To determine the LVEF, the Simpson method was chosen. In the studied sample, on the first day of MI, the mean values of LVEF in the range of 40-49% were determined in 3 (2,5%) patients, in 31 (26%) — LVEF <40%, LVEF ⩾50% was determined in 86 (71,6%) patients. To diagnose DD, the transmitral blood flow was assessed using the following indicators: peak E — the phase of rapid early ventricular filling (normal value of the indicator (N)=58-86 cm/s up to 50 years, 48-86 cm/s >50 years), peak A — the time of atrial contraction (N=30-50 cm/s up to 50 years, 45-73 cm/s >50 years), the ratio of the maximum velocities of the peaks E/A, the time of the flow of early diastolic filling (DT) using pulsed doppler echocardiography , E/Ea is the ratio of the maximum rate of rapid ventricular filling, isovolumic relaxation time of LV (IVRT) (N=70-90 ms). At each stage of the examination (time points 1, 2, and 3), the patients were determined the concentration of PIIINP, the N-terminal fragment of the brain natriuretic propeptide (NT-proBNP) in the venous blood serum, using the enzyme-linked immunosorbent assay with BCM Diagnostics kits (USA). To compare the obtained values of fibrotic markers, a control group was formed, including 20 (100%) healthy volunteers, identical in age (57,9 [52,5; 62,7] years) and gender (men — 15 (75%), women — 5 (25%)) with the studied sample. In the control group, the PIIINP concentration was 7,2 [6,8; 7,5] ng/ml, NT-proBNP ⩽70 pg/ml.

Table 1

Clinical and anamnestic data of STEMI patients included in the final analysis

Indicators	n	%
Female	23	26,7
Male	63	73,3
Smoking	61	71
Diabetes	17	19,8
Obesity (according to WHO classification BMI ⩾30 kg/m^2)	30	34,8
Hypertension	83	96,6
Hypercholesterolemia	28	32,4
Complicated family history of CAD	3	3,5
History of angina pectoris	27	31,5
History of CHF (according to anamnesis)	10	11,7
Postinfarction cardiosclerosis	7	8,3
Atrial fibrillation	6	6,9
Percutaneous coronary intervention (no earlier than one year prior to this study)	5	5,7
Chronic kidney disease	2	2,5
Peripheral artery disease	1	1,3

Note: WHO — World Health Organization, BMI — Body Mass Index.

During the period of hospitalization, patients received therapy in accordance with current national guidelines [6]. For further study, a sample was formed that included patients with LVEF ⩾50% (n=86). Table 1 shows the clinical and anamnestic characteristics of the studied sample. It can be seen that the majority of patients in the studied sample were characterized by the presence of risk factors for cardiovascular diseases; >70% were smokers. At least two thirds suffered from

Table 2

Changes in transmitral blood flow parameters over time during hospitalization and one year after STEMI

Indicators	Examination points			p
	Time point 1	Time point 2	Time point 3	
LVEF (%)	59 [54; 63]	62,0 [56,0; 65,0]*#	53 [47; 56]*	<0,001
E (cm/s)	57,0 [50,0; 70,0]	60,0 [49,0; 73,0]	60 [47; 69]	0,556
A (m/s)	70,0 [60,0; 79,0]	70,0 [58,0; 80,0]*	71 [59; 78]	0,011
E/A	0,80 [0,71; 1,22]	0,79 [0,68; 1,21]	0,77 [0,66; 1,13]	0,896
IVRT (m/s)	107,0 [104,0; 118,0]	106,0 [104,0; 118,0]	106,0 [103,0; 116,0]	0,157
DT (m/s)	196,0 [170,0; 224,0]	189,5 [170,0; 222,0]	210 [176,0; 228,0]	0,092
Em (cm/s)	7,0 [6,0; 8,0]	6,0 [5,0; 8,0]	6,0 [5,0; 8,0]	0,082
E/Em	8,8 [7,6; 11,4]	9,0 [7,5; 10,43]	8,9 [7,5; 10,50]	0,356

Note: * — p <0,05 versus point 1, # — p<0,05 versus point 3. E — phase of rapid early ventricular filling, A — atrial contraction time, E/A — ratio of maximum peak velocities, IVRT — time of isovolumic relaxation of the LV, DT — time of the flow of early diastolic filling, Em is the speed of movement of the lateral part of the fibrous annulus of the mitral valve, E/Em — ratio of the rate of transmitral flow in early diastole to the speed of movement of the lateral part of the annulus of the mitral valve.

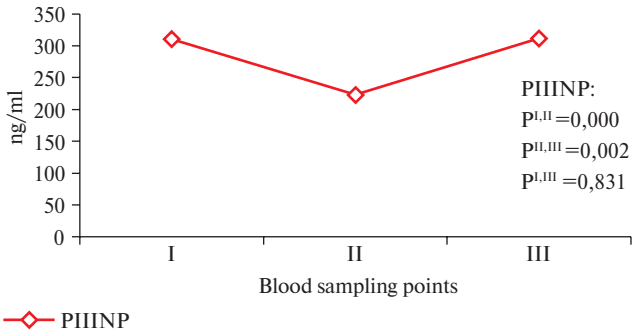

Figure 1 Dynamics of PIIINP concentration during 1 year after STEMI.

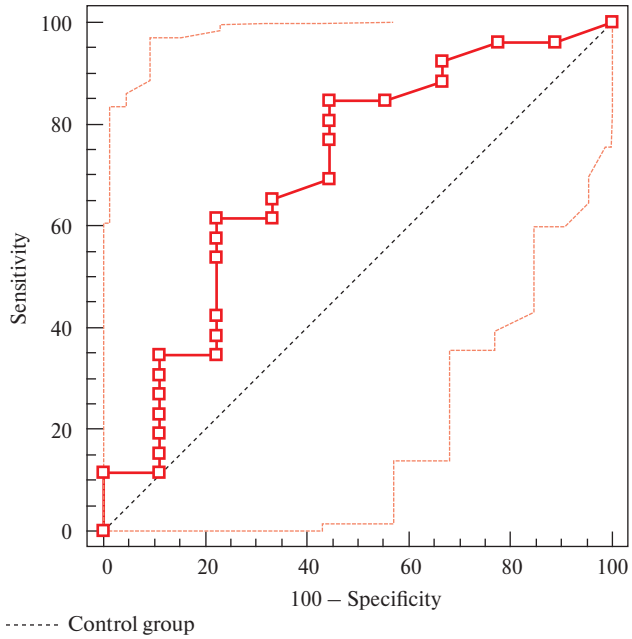

Figure 2 ROC curve for predicting DD during 1 year of follow-up after STEMI.

arterial hypertension for a long time. Hypercholesterolemia was quite often detected (32,5%). Disorders of carbohydrate metabolism accounted for 19,8%. At each stage of the study, the presence and severity of HF was assessed (acute — according to the Killip classification; I — n=76 (88,3%), II — n=8 (9,4%), III — n=2 (2,3%), IV — 0; chronic — according to the NYHA (New-York Heart Association) classification: signs of HF I and II functional classes (FC) were recorded in 84 cases (97,7%), III-IV FC — 2 (2,3%). At the annual stage, the presence of the following endpoints was assessed: death, decompensation of CHF, the presence of repeated hospitalizations for cardiovascular events during the follow-up period.

Statistica 7.0 software was used for statistical data processing. Comparison of two independent groups on a quantitative basis was carried out using the Mann-Whitney U-test. Dynamic changes in indicators in dependent groups were determined using the Wilcoxon test. The presence of a relationship between the variables was determined using the Spearman's rank correlation coefficient. Differences in the comparison groups were considered statistically significant at p<0,05.

Results

By the end of 1 year of follow-up, information on 86 patients was available to the analysis. 1 death was registered due to repeated MI. During the entire follow-up period, emergency hospitalizations for the progression of CAD and decompensation of CHF were noted in 5 (5,8%) cases, of which in 3 (3,5%) cases, there were repeated MI development. Angina pectoris of high FC (III-IV) was observed in 3 patients (3,5%). It should be noted that during the year of follow-up, some patients underwent planned revascularization: percutaneous coronary interventions with stenting were performed in 5 (5,8%) cases and in 1 case — coronary bypass graft.

During the year, patients received disaggregants — in 71%, β-blockers — in 80,3%, angiotensin-converting enzyme inhibitors — in 70,1%, calcium antagonists —

in 67%, nitrates — in 19%, anticoagulants — in 6,4%, statins — in 45% of cases.

Comparison of EF and indicators of transmitral blood flow was carried out between 1, 2 and 3 time points of examination (Table 2). The deterioration of LV systolic function became obvious in the form of a significant decrease in EF one year after the index event relative to the first day of the disease (p=0,018), 15 (17,6%) patients from the group with preserved EF moved to the group with a range of 40-49%. On the first day of MI, 29,1% (n=25) of patients with signs of DD were identified among those with preserved EF. A year later, there was an increase in the number of patients with signs of DD by 10% (n=9).

The concentration of PIIINP underwent changes during the follow-up period (Figure 1). Initially increased (relative to the values of the control group) concentration of this marker on the first day of the disease — 311,2 [220,1; 376,3] ng/ml, decreased by the 12th day of the disease — 223,3 [195,3; 312,1] ng/ml, and almost returned to the initial values at the annual stage of the examination — 312,6 [228,0; 383,8] ng/ml.

Fluctuations in the concentration of the studied indicator turned out to be significant and had highly significant differences both at the stationary stage and a year after the index event. The average value of the PIIINP concentration on the first day of the disease was significantly higher than that of the control group. Further changes in PIIINP concentration were still recorded in the range exceeding the control values.

A different dynamic was revealed when analyzing the concentration of NT-proBNP — a marker of CHF. During the hospitalization, the concentration of this marker did not exceed the reference values and was 98,5 on the first day [83,7; 103] and on the 12th day — 99,4 [87,2; 111,3] pg/ml, without significant differences between 1 and 2 detection points (p=0,127). A year later, the NT-proBNP concentration significantly exceeded the values of the previous determinations and amounted to 124,4 pg/ml (p=0,043).

In order to identify possible links between the echocardiography and the studied fibrotic markers, a correlation analysis was carried out, as a result of which the following statistically significant links were obtained: PIIINP on the first day/E 1 year, r=0,44, p=0,027, PIIINP on the first day/E/Em 1 year, r=0,45, p=0,024.

To determine the predictive value of PIIINP, determined on the first day of MI, in relation to DD one year after the development of the disease, an ROC analysis was performed. When constructing the ROC curve, the threshold level of the marker was selected step by step by the method of concentration selection when the total maximum sensitivity and specificity of the model was reached. As a result of the ROC-analysis, the concentration of PIIINP (on the first day of STEMI) was determined, associated with the risk of developing DD after a year (Figure 2).

Thus, at a PIIINP concentration of ⩾387,8 ng/ml on the first day, the risk of developing DD (p=0,050, sensitivity 84,62%, specificity 55,56%) increases within a year after STEMI with preserved LVEF.

Discussion

In the course of the study, it was possible to identify facts indicating the presence of a relationship between the fibrotic markers PIIINP and echocardiography indicators. This was confirmed by the correlations between the studied marker and the indicators of transmitral blood flow, characterizing the state of the DF of the LV myocardium. PIIINP is a protein formed during the synthesis of type III collagen [7]. According to some scientific sources, an increased concentration of this protein is considered as a predictor of deaths from diseases of the cardiovascular system or repeated hospitalizations due to worsening CHF [8]. Some studies have demonstrated the presence of correlations between the concentration of PIIINP in the blood and the volume fraction of type III collagen in the myocardium obtained during histological study [9].

In the modern scientific literature, there is no information on the presence of a relationship between the concentration of markers of myocardial fibrosis and the fact of the development of DD. According to the ROC analysis, at a PIIINP concentration of ⩾387,8 ng/ml on the first day of MI, the risk of developing DD in a year increase. Based on the data obtained, it can be assumed that an increase in PIIINP concentration is a marker of impaired myocardial relaxation due to a decrease in its elasticity. A similar pattern was obtained in the study [10].

Currently, one of the fundamental reasons for the development of DD is an increase in myocardial stiffness due to its fibrosis. The mechanism of transformation of asymptomatic DD into diastolic HF is still controversial. It is likely that the key link in this process is the imbalance of collagen in the myocardium [11]. It has been proven that the myocardium of a healthy person contains up to 2% of collagen by volume. Collagen type III, like type I, is the main representative of collagen in the myocardium. In addition, type I collagen has been shown to be responsible for stiffness and type III collagen for elasticity. Normally, the concentration of type III collagen prevails over the first type [11]. Collagens of both types are derived from procollagen precursors containing the C-terminal type I procollagen propeptide and PIIINP. The combination of these two types of collagens ensures the functional and structural integrity of cardiomyocytes and contributes to the maintenance of a certain direction of myofibrils in them [12]. Probably, the predominance of the synthesis of collagen types I and III over their breakdown leads to the accumulation of excess fibers, which is a trigger for the formation of myocardial fibrosis with subsequent disruption of DF [12].

The HF on the background of preserved LV systolic function is currently of increased interest among scientists due to its high frequency among patients after an acute coronary event and an unfavorable long-term prognosis. In this work, we managed to determine the value of the PIIINP concentration associated with the risk of developing LV DD and, as a consequence, the progression of CHF. However, it is worth mentioning that according to the results of the annual follow-up, a deviation from the standard treatment was revealed in the form of a low percentage of intake of almost all necessary classes of drugs, including angiotensin-converting enzyme inhibitors, which is due to the low adherence of patients to the prescribed drug treatment. This fact undoubtedly has a negative impact on the formation of LV DD.

For many years, the severity of heart failure has been strongly associated with impaired ventricular systole, the presence of which was judged by the value of LVEF. At the present stage, with the emergence of the myocardial theory of the pathogenesis of CHF, significant, and in most cases fundamental importance in the development and progression of HF, is given to the violation of DF, while emphasizing the great vulnerability of DF, the violation of which always precedes systolic, and in some cases, it can preserve the nature of isolated DF, as the basis of CHF. Determination of the serum NT-proBNP level is considered a standard procedure in the diagnosis of CHF. Previously, it was proved that BNP has a particular pathophysiological significance in the diagnosis of heart failure, in the stratification of the risk of cardiovascular diseases and in the assessment of the effectiveness of treatment of CHF [8]. The results of this study demonstrated a significant increase in the concentration of NT-proBNP in patients a year after the development of STEMI. This fact is a reflection of heart failure progression within a year after MI and, as the results show, including due to DD on the background of increased concentration of the fibrotic markers.

At the same time, the identification of CHF with preserved LVEF is especially important for patients without pronounced clinical manifestations of the disease. These signs include shortness of breath, weakness, tachycardia with preserved LVEF and in the absence of objective signs of HF, which can divert attention to other, non-cardiac causes of symptoms (respiratory pathology, detraining and/or overweight [13]. Despite the disturbing tendencies mentioned above, the question of optimal diagnosis remains open. This situation emphasizes the need for an integrated approach to the study of DF and encourages an active search for new biological markers of its impairment [14].

Conclusion

Within a year after the development of STEMI and preserved LVEF, there is a deterioration in LV systolic function and, in some cases, an aggravation of diastolic function. The threshold value of PIIINP (⩾387,8 ng/ml) was established, determined on the first day of the disease, at which the risk of developing DD increases one year after STEMI. An increase in NT-proBNP concentration one year after STEMI indicates the progression of heart failure.

Relationships and Activities: none.

References

1. Titova AL, Saiganov SA. Diastolic function of the left ventricle in patients with coronary heart disease who underwent coronary artery bypass surgery. Russian family doctor. 2014;18(3):10-7. (In Russ.)
2. Bartosh FL, Bartosh LF, Adonina TS. Features of diastolic function of the left ventricular myocardium in patients with hypertension with atrial fibrillation. Arterial hypertension. 2012;18(2):142-7. (In Russ.) doi:10.18705/1607-419X-2012-18-2-142-147.
3. Shilov SN, Teplyakov AT, Yakovleva IL, et al. Clinical and pathogenetic relationship of chronic heart failure, type 2 diabetes mellitus and osteoporosis. Complex problems of cardiovascular diseases. 2018;7(1):6-13. (In Russ.) doi:10.17802/2306-1278-2018-7-1-6-1.
4. Weber K, Sun Y, Campbell S. Structural remodeling of the heart by fibrous tissue: Role of circulating hormones and locally produced peptides. Eur Heart J. 1995;16 Suppl N:12-8. doi:10.1093/eurheartj/16.suppl_n.12.
5. Karetnikova VN, Kashtalap VV, Kosareva SN, Barbarash OL. Myocardial fibrosis: current aspects of the problem. Therapeutic Archive. 2017;89(1):88-93. (In Russ.) doi:10.17116/terarkh201789188-93.
6. Mareev VYu, Ageev FT, Arutyunov GP, et al. National recommendations of the OSSN, RKO and RNMOT for the diagnosis and treatment of CHF (fourth revision). J Heart Fail. 2013;14(7)(81):379-472. (In Russ.)
7. Drapkina OM, Zyatenkova EV. Markers of fibrosis in patients with metabolic syndrome. Russian Medical J. 2016;26:1727-31. (In Russ.)
8. Belenkov YuN, Oganov RG. Cardiology: national leadership. M.: GEOTAR-Media, 2012. p. 535. (In Russ.) ISBN: 978-5-9704-2733-0.
9. Matyal R, Skubas NJ, Shernan SK, Mahmood F. Perioperative assessment of diastolic dysfunction. Anesth Analg. 2011;113(3):449-72. doi:10.1213/ANE.0b013e31822649ac.
10. Drapkina OM, Gegenava BB. Type III procollagen N-terminal propeptide as a possible serum marker of myocardial fibrosis in patients with type 2 diabetes. Cardiovascular Therapy and Prevention. 2018;17(3):17-21. (In Russ.) doi:10.15829/1728-8800-2018-3-17-21.
11. Drapkina OM, Zyatenkova EV. Assessment of the level of N-terminal collagen type III propeptide in patients with chronic heart failure and metabolic syndrome. Cardiovascular Therapy and Prevention. 2015;14(6):42-7. (In Russ.) doi:10.15829/1728-8800-2015-6-42-47.
12. Putyatin AN, Kim LB. Extracellular matrix of the heart and postinfarction reparative fibrosis (part 1). Vestnik SAFU. Series: Biomedical Sciences. 2016;4:54-66. (In Russ.) doi:10.17238/issn2308-3174.2016.4.54.
13. Kovar F, Knazeje M, Mokan M. Risk Stratification and Invasive Strategy in NSTE-ACS [Electronic Resource]. URL: http://cdn.intechopen.com/pdfs/19478/InTech-Risk_stratification_and_invasive_strategy_in_nste_acs.pdf (date access: 25.09.2013).
14. Mrikaev DV. Diastolic dysfunction of the left ventricle in patients with heart failure. Creative cardiology. 2017;11(2):145-58. (In Russ.) doi:10.24022/1997-3187-2017-11-2-145-158.