Медицинская иммунология
2021, Т. 23, № 4,
стр. 839-844

Краткие сообщения
Short communications

Medical Immunology (Russia)/
Meditsinskaya Immunologiya
2021, Vol. 23, № 4, pp. 839-844

ДИНАМИКА БИОМАРКЕРОВ КАРДИОВАСКУЛЯРНОГО РИСКА И ЦИТОКИНОВ У БОЛЬНЫХ С ДЕКОМПЕНСИРОВАННОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ С СИСТОЛИЧЕСКОЙ ДИСФУНКЦИЕЙ ИШЕМИЧЕСКОГО ГЕНЕЗА ПРИ НАЛИЧИИ И ОТСУТСТВИИ МИОКАРДИТА

Огуркова О.Н.[1], Кручинкина Е.В.[1], Гусакова А.М.[1], Суслова Т.Е.[1], Рябов В.В.[1, 2]

[1] Научно-исследовательский институт кардиологии ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия
[2] ФГБОУ ВО «Сибирский государственный медицинский университет» Министерства здравоохранения РФ, г. Томск, Россия

Резюме. Развитие и прогрессирование сердечной недостаточности связано с различными патофизиологическими механизмами, особый интерес представляет изучение воспалительной реакции, как фундаментального звена в патогенезе ХСН и ее основного компонента – декомпенсации. Проведено открытое, нерандомизированное, проспективное исследование по изучению клинико-морфологических особенностей субклинического воспаления у больных с острой декомпенсацией ишемической хронической сердечной недостаточностью со сниженной фракцией выброса. В исследование были включены 25 больных с декомпенсацией ишемической ХСН с ФВ левого желудочка < 40% в возрасте от 35 до 75 лет (60,12±9,3) с подписанным информированным согласием. В данном исследовании изучалась динамика содержания в сыворотке крови С-реактивного белка (СРБ), N-концевого фрагмента белка-предшественника мозгового натрийуретического пептида (NT-proBNP), растворимого ST2 (sST2), рецептора инсулиноподобного фактора роста 1 (IGF-1R), интерлейкина-6 (IL-6), интерлейкина-10 (IL-10), фактора некроза опухоли-α (TNFα) на Multiplex Instrument FLEXMAP 3D Luminex Corporation. Все обследованные пациенты были разделены на две группы в зависимости от диагностированного миокардита: пациенты без признаков миокардита и пациенты с миокардитом. Установлено, что в группе пациентов с диагностированным миокардитом наблюдалось повышенное содержание СРБ, IGF-1R, IL-6 и IL-10, TNFα по сравнению с группой пациентов без миокардита. Средние концентрации NT-proBNP и sST2 в обеих группах не различались. При последующем визите через год наблюдалось снижение содержания СРБ, NT-proBNP, IL-6 в обеих группах. В группе больных миокардитом наблюдалось повышение содержания sST2, IGF-1R, IL-10. Таким образом, проведенное в динамике исследование выявило достоверные различия в изменении сывороточной активности про- и противовоспалительных цитокинов и биомаркеров сердечно-сосудистого риска у пациентов с декомпенсированной сердечной недостаточностью с систолической дисфункцией при диагностированном миокардите и при его отсутствии.

Ключевые слова: воспаление, цитокины, биомаркеры, сердечная недостаточность, миокардит

Адрес для переписки:
Огуркова Оксана Николаевна
Научно-исследовательский институт кардиологии
634012, Россия, г. Томск, ул. Киевская, 111а.
Тел.: 8 (960) 975-45-44.
E-mail: ogurkovaon@mail.ru

Address for correspondence:
Ogurkova Oksana N.
Cardiology Research Institute
634012, Russian Federation, Tomsk, Kievskaya str., 111a.
Phone: 7 (960) 975-45-44.
E-mail: ogurkovaon@mail.ru

Образец цитирования:
О.Н. Огуркова, Е.В. Кручинкина, А.М. Гусакова, Т.Е. Суслова, В.В. Рябов «Динамика биомаркеров кардиоваскулярного риска и цитокинов у больных с декомпенсированной сердечной недостаточностью с систолической дисфункцией ишемического генеза при наличии и отсутствии миокардита» // Медицинская иммунология, 2021. Т. 23, № 4. С. 839-844.
doi: 10.15789/1563-0625-DCI-2280

For citation:
O.N. Ogurkova, E.V. Kruchinkina, A.M. Gusakova, T.E. Suslova, V.V. Ryabov "Dynamic changes in cardiovascular risk biomarkers and cytokines of myocarditis-free patients with decompensated heart failure and ischemic systolic dysfunction", Medical Immunology (Russia)/ Meditsinskaya Immunologiya, 2021, Vol. 23, no. 4, pp. 839-844.
doi: 10.15789/1563-0625-DCI-2280
DOI: 10.15789/1563-0625-DCI-2280

DYNAMIC CHANGES IN CARDIOVASCULAR RISK BIOMARKERS AND CYTOKINES OF MYOCARDITIS-FREE PATIENTS WITH DECOMPENSATED HEART FAILURE AND ISCHEMIC SYSTOLIC DYSFUNCTION

Ogurkova O.N.[a], Kruchinkina E.V.[a], Gusakova A.M.[a], Suslova T.E.[a], Ryabov V.V.[a, b]

[a] *Cardiology Research Institute, Tomsk National Research Medical Centre, Russian Academy of Sciences, Tomsk, Russian Federation*
[b] *Siberian State Medical University, Tomsk, Russian Federation*

Abstract. The development and progression of heart failure is associated with a variety of pathophysiological mechanisms, of particular interest is the study of the inflammatory response as a fundamental link in the pathogenesis of CHF and its main component – decompensation. An open, non-randomized, prospective study was carried out to evaluate the clinical and morphological features of subclinical inflammation in patients with acute decompensation of ischemic chronic heart failure with a reduced ejection fraction. The study included 25 patients with decompensated ischemic CHF with left ventricular ejection fraction < 40% aged 35 to 75 years (60.12±9.3 y. o.). In this study the dynamics of the serum content of C-reactive protein (CRP), N-terminal fragment of the brain natriuretic peptide precursor protein (NT-proBNP), soluble ST2(sST2), insulin-like growth factor-1 receptor (IGF-1R), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-α (TNFα) was performed by multiplex immunoassay using the FLEXMAP 3D. All studied patients were divided into two groups depending on the diagnosed myocarditis: patients with no signs of myocarditis and patients with myocarditis. It was found that in the group of patients with diagnosed myocarditis there was an increased content of CRP, IGF-1R, IL-6 and IL-10, TNFα compared to the group of patients without myocarditis. The median concentrations of the NT-proBNP and sST2 in both groups did not differ. At the follow-up visit a year later, there was a decrease in the content of CRP, NT-proBNP, IL-6 in both groups. In the group of patients with myocarditis, an increase in the content of sST2, IGF-1R, IL-10 was observed. Thus, the study carried out in dynamics revealed significant differences in the degree of changes in the serum activity of pro- and anti-inflammatory cytokines and biomarkers of cardiovascular risk in patients with decompensated heart failure with systolic dysfunction with diagnosed myocarditis and in its absence.

Keywords: inflammation, cytokines, biomarkers, heart failure, myocarditis

Introduction

Decompensation of CHF is a serious clinical and public health problem with a high level of morbidity, mortality and rate of hospitalizations [6]. The development and progression of heart failure are associated with a variety of pathophysiological mechanisms, of particular interest is examining an inflammatory response as a fundamental link in the CHF pathogenesis and its main component – decompensation [7]. An inflammatory concept has been formulated, which is based on the persistent inflammation present at the early stages of CHF, as well as at later stages, when CHF is verified [6]. Recently, the study of inflammation markers and their role in cardioprotective mechanisms, as well as growth factors and cytokines as prognostically relevant biomarkers of developing heart failure deserved particular interest [4, 5]. It is known that imbalance of pro- and anti-inflammatory cytokines significantly contributes to development and progression of CHF, but the results of experimental and exploratory clinical studies have not led to the emergence of a single effective anti-inflammatory strategy in CHF syndrome [7].

Purpose of the study: to study the dynamics and relationship of serum cardiovascular risk biomarkers and cytokines in patients with decompensated heart failure with ischemic systolic dysfunction with/without myocarditis using xMAP technology.

Materials and methods

An open, non-randomized, prospective study was carried out to evaluate the clinical and morphological features of subclinical inflammation in patients with acute decompensation of ischemic chronic heart failure with reduced ejection fraction. This study is registered at the ClinicalTrials.gov, ID: NCT02649517. The study included 25 patients with decompensated ischemic CHF with left ventricular ejection fraction < 40% aged 35 to 75 years (60.12±9.3 y.o.), who signed informed consent, 6 months after successfully performed angioplasty and/or coronary artery bypass grafting. The therapy performed in patients at the time of enrolling to the study corresponded to the

current recommendations such as: beta-blockers, diuretics, mineralocorticoid receptor antagonists, cardiac glycosides. Exclusion criteria were: acute coronary syndrome less than 6 months before hospitalization; hemodynamically significant valvular heart disease; severe concomitant diseases that could affect the course of the underlying disease and the study results. All patients underwent invasive coronary angioplasty to exclude the progression of coronary artery atherosclerosis, as well as endomyocardial biopsy with immunohistological analysis to verify myocarditis. This article analyzes the dynamics of biomarkers in such patients by using Milliplex kit (Merck KGaA, Darmshdadt) (n = 10). The diagnosis of myocarditis was established in 5 patients according to immunohistochemical criteria: the presence of at least 14 leukocytes/mm^2, with the presence of CD3 positive T-lymphocytes ≥ 7 cells/mm^2. Fasting blood sampling for biomarkers from the cubital vein was carried out during hospitalization of patients and one year later at the checkpoint visit. The evaluation serum of high-sensitive C-reactive protein (hCRP) concentration was carried out in blood serum by ELISA (Biomedica); level of N-terminal fragment of brain natriuretic peptide precursor protein (NT-proBNP) pg/ml was determined using Human Cardiovascular Disease Panel 1. Levels of soluble ST2 (sST2) ng/ml, insulin-like growth factor-1 receptor (IGF-1R) pg/ml were investigated by using Human Cardiovascular Disease Panel 5. The level of interleukin-6 (IL-6) pg/ml, interleukin-10 (IL-10) pg/ml, tumor necrosis factor-α (TNFα) pg/ml was measured by using Human Cytokines/Chemokines-38 kit. All studies were performed using Multiplex Instrument FLEXMAP 3D Luminex Corporation and MILLIPLEX Analyst 5.1 software (Merck KGaA, Milliplex; Darmshdadt), the Core Facility "Medical genomics", Tomsk NRMC.

Results and discussion

All patients were divided into two groups depending on the diagnosed myocarditis: patients with no signs of myocarditis were included in group 1 and patients with myocarditis were included in group 2. Clinical characteristics are presented in Table 1. Examining serum biomarkers from patients during hospitalization showed that in the group of patients with diagnosed myocarditis, there was an increased content of C-reactive protein, insulin-like growth factor receptor-1, interleukins-6 and 10, tumor necrosis factor -α compared to the group of patients without myocarditis. The median NT-proBNP concentration in both groups was comparable and exceeded the pathologically significant level of 125 pg/ml. The sST2 level in both groups was also comparable on admission, but did not exceed the pathologically significant level of 30 ng/ml. The data are presented in Table 2. A decreased level of C-reactive protein was noted in both groups, at the follow-up visit one year later in patients without myocarditis, the observed decrease was by 58%, while in the group with diagnosed myocarditis it was decreased only by 28%. The NT-proBNP content in both groups decreased by 40% one year later, but its concentration also remained above the pathologically significant level. The level of sST2 one year later in the group of patients without myocarditis remained unchanged; in the group of patients with myocarditis, it was increased by 76%. In the group of patients with myocarditis, the IGF-1R content increased by 5-fold, while the median IGF-1R concentration in the blood serum of patients without myocarditis remained at the level comparable to that observed at the time of hospitalization. The content of interleukin-6 in both groups of patients decreased by 48 and 43%, respectively. The content of interleukin-10 in the group of patients with myocarditis increased by 18% compared to the baseline level; in the group of patients without myocarditis, the level of IL-10 remained unchanged. In both groups, the content of TNFα decreased by 12 and 20%, respectively. Thus, the study of the dynamics of biomarkers in both groups revealed decreased concentrations of inflammation markers such as CRP, IL-6, and NT-proBNP a marker of the risk of heart failure after 12 months of observation. Moreover, in the group of patients with myocarditis, there was increased content of sST2, IGF-1R, IL-10 after 12 months of observation. Correlation analysis in the group of patients without myocarditis revealed a negative relationship between the content of NT-proBNP and IGF-1R ($r = -0.70$, $p < 0.05$). In both groups of patients, a positive relationship with high correlation coefficient was found between serum level of sST2 and IGF-1R ($r = 0.90$) $p < 0.05$ on admission and at the follow-up visit one year later.

Cytokines are a key element of the immune system in the development of acute and chronic inflammation. The majority of chronic inflammatory diseases, regardless of their organ location, are based on imbalanced production between pro- and anti-inflammatory mediators [4]. Therefore, the basis for the treatment of any inflammatory process is attempted to normalize it by any means. It has now been established that not only lymphocytes and macrophages, but also other cells are capable of synthesizing cytokines, and in this respect the heart is a unique source of their production [9]. The concentration of hCRP is considered as the most sensitive and specific laboratory marker of inflammation and tissue damage [8] and, as we demonstrated in our study, it correlates with the synthesis of IL-6 both with/without myocarditis, which, in turn, plays an important role in the developing inflammation. It is known that cardiomyocytes in patients with heart failure produce

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS WHO WERE INCLUDED IN THE STUDY, Me ($Q_{0.25}$-$Q_{0.75}$)

Parameters	Group 1 (n = 5)	Group 2 (n = 5)
Age, years	58.0 (51.0-61.0)	61.0 (56.0-67.0)
Body Mass Index, kg/m²	31.6 (30.3-34.7)	28.0 (25.30-31.07)
Duration of chronic heart failure, month	24.0 (12.7-77.0)	12.0 (8.0-48.0)
Time between the last myocardial infarction before the development of chronic heart failure, month	26.0 (6.0-114.0)	80.0 (13.0-120.0)
Functional class of CHF by (NYHA) before hospitalization:		
II	4	2
III	–	3
IV	1	–
Systolic pressure, mmHg	130.0 (100.0-138.0)	120.0 (100.0-130.0)
Diastolic pressure, mmHg	80.0 (60.0-80.0)	70.0 (60.0-80.0)
Heart rate, beats/min.	68.0 (64.0-82.0)	72.0 (68.0-90.0)
Respiratory rate, breath/min.	18.0 (17.0-20.0)	18.0 (16.0-20.0)
Medical treatment during hospitalization:		
A2 receptor Blockers/ ACE inhibitors	–	1
Beta-blockers	3	–
Cardiac glycosides	-	2
Diuretics	4	4
Acyclovir	–	2
Viferon	1	4

TABLE 2. CYTOKINE LEVEL, Me ($Q_{0.25}$-$Q_{0.75}$)

	Baseline		At 12 mounts	
Parameter	**Group 1 (n = 5)**	**Group 2 (n = 5)**	**Group 1 (n = 5)**	**Group 2 (n = 5)**
C-RP(h) mg/l	6.59** (1.03-9.66)	8.26 (1.34-10.20)	2.77 (1.99-4.32) *p = 0.06	5.93 (1.69-10.46)
Nt-proBNP pg/ml	579.70 (93.13-683.71) **p = 0.06	525.31 (212.34-532.80) **p = 0.06	362.12 (163.79-656.05)	323.40 (268.72-625.72)
sST2 ng/ml	2.22 (1.83-4.38)	2.14** (1.35-3.36)	2.10* (1.83-6.54)	8.58 (5.90-10.98)
IGF-1R pg/ml	6639.96 (4213.32-7839.19)	8245.50** (7275.64-8819.10)	7758.29* (5552.64-15202.21)	39808.16 (23040.85-95407.03)
IL-6 pg/ml	6.79 (4.69-7.05) **p = 0.06	8.11 (5.33-9.80) **p = 0.06	3.50 (3.48-6.87)	4.60 (4.02-8.84)
IL-10 pg/ml	1.70 (1.28-2.41)	2.57 (0.92-3.60)	1.55* (1.23-2.10)	3.16 (3.09-6.25)
TNFα pg/ml	7.62* (4.98-12.65)	20.46 (19.53-23.90)	6.71* (6.42-11.60)	16.53 (11.60-17.81)

Note. *, statically significant within the group 1 *vs* 2; **, statically significant within the group Baseline *vs* At 12 mounts; Group 1, there is no myocarditis; Group 2, there is myocarditis.

TNFα, even without manifested inflammatory process. In addition, TNFα induces the process of cardiomyocyte programmed death, which loses its compensatory character under the pathological conditions posing TNFα as having fundamental importance in myocardial remodeling. [8]. In our study, an increased content of serum TNFα was noted in the group of patients with myocarditis; after 12 months of observation, its level remained unchanged, whereas content of interleukin 10 tendned to increase. It is known that the anti-inflammatory cytokine IL-10 can inhibit TNFα production and counterbalance its negative effects in heart failure [2]. However, the results of clinically examined IL-10 in heart failure and its progression are controversial. On the one hand, there is an evidence of decreased IL-10 levels in HF and left ventricular remodeling; on the other hand, there are reports showing its increased levels and elevated mortality in HF patients with a simultaneous increased IL-10 and TNFα concentrations [1]. IL-10 can function as a component of the feedback mechanism: elevated levels of TNFα in HF stimulate the secretion of IL-10, and IL-10, on the contrary, suppresses excessive activity of pro-inflammatory cytokines; however, a role of IL-10 regardless of TNFα, cannot be ruled out as the production of IL-10 is induced together with pro-inflammatory cytokines, TNFα in particular in inflammatory processes and in HF [3]. It was supported by showing positive correlations between the content of TNFα and IL-10 ($r = 0.70$) $p < 0.05$ in the group of patients with myocarditis. Among diverse existing modern biochemical markers, natriuretic peptides have been introduced into routine clinical practice, proving to act as markers of myocardial stress, myocardial dysfunction and heart failure [9]. Currently, not a single biomarker can account for all aspects of CHF syndrome and development of its decompensation [9]. According to the numerous modern studies, sST2 has recently been included in the European and American guidelines for CHF treatment. The data obtained in the group of patients with diagnosed myocarditis after 12 months of observation demonstrate not only increased serum sST2 content, but also a positive relationship with proinflammatory cytokines. It is possible that the level of sST2 expression not only confirms the inflammatory mechanism of CHF development, but also reflects the activity of systemic inflammatory response upon disease progression. In recent years, the association of IGF-1 with cardiovascular diseases as an independent risk factor has been discussed, but the results of these studies are rather contradictory. IGF-1 under the influence of growth hormone is secreted in the liver as well as also produced in cardiomyocytes, smooth muscle cells and fibroblasts; it is capable of exerting an insulin-like metabolic effect that exerts a significant role in regulating the structure and function of the myocardium and blood vessels [1]. There is evidence that decreased synthesis of IGF-1 promotes enhanced apoptosis of cardiomyocytes and progression of myocardial fibrosis that appears to be a predictor of decompensated chronic heart failure [3,9]. IGF-1 exerts its action through ubiquitously expressed receptors (IGF-1R) including cardiomyocytes, which determines their role as modulators of myocardial structure and function. Insulin-like growth factors in the bloodstream are associated with proteins that play a key role in the bioavailability of ligands, as they compete with IGF-1R for IGF-I. By binding to IGF-1, IGFPs thereby inhibit proliferation signals and, according to the feedback loop, IGF-1R becomes elevated if IGF-1R is over-activated. There is evidence that proinflammatory cytokines can be involved in blocking IGF-1 specific receptor binding due to the phosphorylation of serine residues in IRS [9]. It is possible that the significant increase in the IGF-1R content obtained in our study in the group of patients with myocarditis underlies hormonal and neurohumoral processes and serves as a biochemical marker of altered metabolic processes, whereas established positive relationships with inflammation markers seem to be a predictor of aggravated chronic heart failure decompensation, indicating an unfavorable prognosis. Thus, a study in the dynamics of biomarkers in patients with diagnosed myocarditis demonstrated increased level of IGF-1R, soluble ST2, IL-10, a decrease in NL-6, NT-proBNP and C-reactive protein and their close inter-relationship. In the group of patients without myocarditis, there was a decrease in IL-6, NT-proBNP and C-reactive protein, the levels of other biomarkers remained unchanged. The follow-up study revealed significant differences in magnitude of changes in serum level of pro- and anti-inflammatory cytokines and biomarkers of cardiovascular risk in patients with decompensated heart failure with systolic dysfunction with/without diagnosed myocarditis. The established relationships allow us to assume that the presence of myocarditis in patients with decompensated heart failure with ischemic systolic dysfunction leads to formation of more unfavorable relationships in the feedback loop of cytokine secretion, leading to evenly greater shift in the cytokine balance towards quantitative predominance of pro-inflammatory cytokines.

References

1. Gennadinik A.G., Nelaeva A.A. The role of insulin-like growth factor-I in metabolism, regulation of cell renewal and aging processes. *Obesity and Metabolism, 2010, no. 2, pp. 10-15.* (In Russ.)
2. Grakova E.V., Teplyakov A.T., Kopyeva K.V., Akhmedov Sh.D., Ogurkova O.N., Soldatenko M.V. Prediction role of a novel biomarker ST2 in risk assessment of adverse cardiovascular events in chronic heart failure with preserved and intermediate ejection fraction after myocardial revascularization. *Cardiovascular Therapy and Prevention, 2018, Vol. 17, no. 5, pp. 40-46.* (In Russ.)
3. Grakova E.V., Kopieva K.V., Teplyakov A.T., Ogurkova O. N., Soldatenko M. V., Garganeeva A. A. Clinical use of the new biomarker ST2 in patients with chronic heart failure of ischemic genesis: an exercise test. *Cardiovascular Therapy and Prevention, 2019, Vol. 18, no. 4, pp. 12-18.* (In Russ.)
4. Grigoryan S.V., Adamyan K.G., Azarapetyan L.G. The role of inflammatory markers in atrial fibrillation: a review. *Cardiovascular Therapy and Prevention, 2012, Vol. 11, no. 5, pp. 74-78.* (In Russ.)
5. Kamardinov D.Kh., Songurov R.N., Ioshina V.I., Buziashvili Yu.I. Soluble ST2 – as a biomarker, risk stratification tool, and therapeutic target in patients with chronic heart failure. *Cardiology, 2020, Vol. 60, no. 2, pp. 111-121.* (In Russ.)
6. Kruchinkina E.V., Ryabova T.R., Rogovskaya Yu.V., Batalov R.E., Ryabov V.V. The incidence and profile of cardiotropic viral agents in the myocardium in patients with decompensated chronic heart failure with systolic dysfunction of ischemic origin. *Siberian Medical Journal, 2017, Vol. 32, no.1, pp. 46-49.* (In Russ.)
7. Kruchinkina E.V., Ryabov V.V. Immune response in decompensation of ischemic chronic heart failure. *Russian Journal of Cardiology, 2018, Vol. 1, no. 153, pp. 72-77.* (In Russ.)
8. Serik S.A., Chenchik T.A., Serdobinskaya-Kanivets E.N., Bondar T.N. Interleukin-10 and pro / anti-inflammatory cytokine balance in heart failure in patients with type 2 diabetes mellitus. *Ukrainian Therapeutic Journal, 2012, no. 3-4, pp. 58-63.* (In Russ.)
9. Zakirova A.N., Fatkullina E.Z., Zakirova N.E., Zhamalov L.M. Insulin-like growth factor-1 and myocardial remodeling in patients with arterial hypertension and metabolic syndrome. *Rational Pharmacotherapy in Cardiology, 2015, Vol. 11, no. 5, pp. 489-495.* (In Russ.)

Авторы:

Огуркова О.Н. *— к.м.н., научный сотрудник отделения клинической лабораторной диагностики, Научно-исследовательский институт кардиологии ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия*

Кручинкина Е.В. *— младший научный сотрудник отделения неотложной кардиологии, Научно-исследовательский институт кардиологии ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия*

Гусакова А.М. *— к.фарм.н., научный сотрудник отделения клинической лабораторной диагностики, Научно-исследовательский институт кардиологии ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия*

Суслова Т.Е. *— к.м.н., руководитель отделения клинической лабораторной диагностики, Научно-исследовательский институт кардиологии ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия*

Рябов В.В. *— д.м.н., заместитель директора по научной и лечебной работе, Научно-исследовательский институт кардиологии ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук»; заведующий кафедрой кардиологии ФПК и ППС ФГБОУ ВО «Сибирский государственный медицинский университет» Министерства здравоохранения РФ, г. Томск, Россия*

Authors:

Ogurkova O.N., *PhD (Medicine), Research Associate, Department of Clinical Laboratory Diagnostics, Cardiology Research Institute, Tomsk National Research Medical Centre, Russian Academy of Sciences, Tomsk, Russian Federation*

Kruchinkina E.V., *Junior Research Associate, Department of Emergency Cardiology, Cardiology Research Institute, Tomsk National Research Medical Centre, Russian Academy of Sciences, Tomsk, Russian Federation*

Gusakova A.M., *PhD (Pharmacology), Research Associate, Department of Clinical Laboratory Diagnostics, Cardiology Research Institute, Tomsk National Research Medical Centre, Russian Academy of Sciences, Tomsk, Russian Federation*

Suslova T.E., *PhD (Medicine), Head, Department of Clinical Laboratory Diagnostics, Cardiology Research Institute, Tomsk National Research Medical Centre, Russian Academy of Sciences, Tomsk, Russian Federation*

Ryabov V.V., *PhD, MD (Medicine), Deputy Director for Research and Clinical Services of Cardiology Research Institute, Tomsk National Research Medical Centre, Russian Academy of Sciences; Head, Cardiology Department of the Continuous Medical Education Faculty, Siberian State Medical University, Tomsk, Russian Federation*

Поступила 15.03.2021
Отправлена на доработку 01.06.2021
Принята к печати 09.06.2021

Received 15.03.2021
Revision received 01.06.2021
Accepted 09.06.2021