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The role of markers of endothelial dysfunction in the pathogenesis of coronary microvascular dysfunction in patients with non-obstructive coronary artery disease

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ABSTRACT

Aim. To study the potential of non-invasive biomarkers in the diagnosis of coronary microvascular dysfunction (CMD) and prediction of the course of heart failure with preserved ejection fraction (HFpEF) in non-obstructive coronary artery disease.

Materials and methods. The 12-month observational study included 118 consecutive patients (6 patients dropped out of the study due to contact loss) with non-obstructive coronary artery disease (CAD) and HFpEF (62 [59; 64]%). At the beginning of the study, serum levels of several biomarkers were assessed using the enzyme immunoassay: N-terminal pro-B-type natriuretic peptide (NT-proBNP), vascular endothelial growth factor (VEGF), and endothelin-1. Coronary flow reserve (CFR) was examined using dynamic single photon emission computed tomography. In the absence of obstructive CAD, CMD was defined as a global decrease in CFR ≤ 2. Echocardiography was used to determine parameters of hemodynamics, LV diastolic dysfunction, and myocardial stress. LV global longitudinal strain (GLS) was assessed using 2D speckle tracking.

Results. The patients were divided into groups depending on the presence of CMD: group 1 included patients with CMD (n = 43), group 2 included those without it (n = 75). In patients in group 1, serum levels of endothelin-1 were 1.9 times higher (p = 0.012), levels of VEGF were 2.16 times higher (p = 0.008), and the concentration of NT-proBNP was 2.6 times higher (p = 0.004) than in patients in group 2. According to the ROC analysis, the concentrations of endothelin-1 ≥ 6.9 pg / ml (AUC = 0.711; p = 0.040) and VEGF ≥ 346.7 pg / ml (AUC = 0.756; p = 0.002) were considered as markers associated with the presence of CMD in patients with non-obstructive CAD. The multivariate regression analysis showed that only the presence of CMD (odds ratio (OR) 2.42; 95% confidence interval (95% CI) 1.26–5.85; p < 0.001) and an increase in NT-proBNP ≥ 760.5 pg / ml (OR 1.33; 95% CI 1.08–3.19; p = 0.023) were factors associated with adverse events, and their combination increased the risk of HFpEF progression by more than 3 times (OR 3.18; 95% CI 2.76–7.98; p < 0.001), whereas markers of endothelial dysfunction were not independent predictors.

Conclusion. Endothelin-1 ≥ 6.9 pg / ml and VEGF ≥ 346.7 pg / ml can be used as non-invasive markers for the diagnosis of CMD. However, markers of endothelial dysfunction were not independent predictors of HFpEF progression in patients with non-obstructive CAD during 12-month follow-up.

Keywords: coronary microvascular dysfunction, endothelial dysfunction, heart failure, preserved ejection fraction, non-obstructive coronary artery disease

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Роль маркеров эндотелиальной дисфункции в патогенезе коронарной микроваскулярной дисфункции у пациентов с необструктивным поражением коронарных артерий

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РЕЗЮМЕ

Цель. Изучение потенциала неинвазивной биомаркерной диагностики коронарной микроваскулярной дисфункции (КМД) и прогнозирования течения сердечной недостаточности с сохраненной фракцией выброса (СНсФВ) при необструктивном атеросклеротическом поражении коронарного русла.

Материалы и методы. В 12-месячное обсервационное исследование последовательно было включено 118 пациентов (шесть пациентов выбыло из исследования по причине утери контакта) с необструктивным поражением коронарных артерий (КА) и сохраненной фракцией выброса левого желудочка (ЛЖ) (62 [59; 64]%). В начале исследования с помощью иммуноферментного анализа в сыворотке крови оценивали уровень некоторых биомаркеров: N-концевого пропептида натрийуретического гормона B-типа (NT-proBNP), VEGF- васкулоэндотелиального фактора роста (VEGF) и эндотелина-1. Резерв коронарного кровотока (CFR) исследовали в ходе динамической однофотонной эмиссионной компьютерной томографии. В отсутствии обструктивного поражения КА, КМД определяли как глобальное снижение CFR ≤ 2. С помощью эхокардиографии определяли параметры гемодинамики, диастолической дисфункции ЛЖ и миокардиального стресса. Глобальная продольная деформация ЛЖ (GLS) оценивалась с помощью 2D-speckle tracking.

Результаты. Пациенты были разделены на группы в зависимости от наличия КМД: в группу 1 вошли пациенты с КМД (n = 43), в группу 2 – больные без нее (n = 75). У больных в группе 1 сывороточные концентрации эндотелина-1 были выше в 1,9 раза (p = 0,012), VEGF – в 2,16 (p = 0,008), а NT-proBNP – выше в 2,6 раза (p = 0,004) по сравнению с больными в группе 2. По данным ROC-анализа, концентрации эндотелина-1 ≥ 6,9 пг/мл (AUC = 0,711; p = 0,040) и VEGF ≥ 346,7 пг/мл (AUC = 0,756; p = 0,002) были идентифицированы как маркеры, связанные с наличием КМД у больных с необструктивным поражением КА. Многофакторный регрессионный анализ показал, что только наличие КМД (отношение шансов (ОШ) 2,42; 95%-й доверительный интервал (95% ДИ) 1,26–5,85; p < 0,001) и повышение уровня NT-proBNP ≥ 760,5 пг/мл (ОШ 1,33; 95% ДИ 1,08–3,19; p = 0,023) являлись факторами, связанными с неблагоприятными событиями, а их сочетание увеличивало риск прогрессирования СНсФВ более чем в 3 раза (ОШ 3,18; 95% ДИ 2,76–7,98; p < 0,001), тогда как маркеры эндотелиальной дисфункции не являлись независимыми предикторами.

Заключение. Уровни эндотелина-1 ≥ 6,9 пг/мл) и VEGF ≥ 346,7 пг/мл могут быть использованы как неинвазивные маркеры для диагностики КМД. Однако маркеры эндотелиальной дисфункции не являлись независимыми предикторами прогрессировании СНсФВ у пациентов с необструктивным поражением КА в течение 12 мес наблюдения.

Ключевые слова: коронарная микроваскулярная дисфункция, эндотелиальная дисфункция, сердечная недостаточность, сохраненная фракция выброса, необструктивное поражение коронарных артерий

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Работа выполнена в рамках фундаментального научного исследования «Изучение механизмов структурного и функционального ремоделирования миокарда при разных фенотипах хронической сердечной недостаточности ишемической и неишемической этиологии» № 122020300045-5.

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INTRODUCTION

Coronary microvascular dysfunction (CMD) plays an essential role in the mechanisms of obstructive and non-obstructive coronary artery disease, as well as their complications, including heart failure with preserved ejection fraction (HFpEF) [1–8]. Studies of the last few years have shown that the presence of CMD is an early marker of cardiovascular diseases and is closely associated with higher incidence of adverse clinical outcomes compared to individuals without such microcirculatory disorders [2, 3]. In the meantime, the results of studies by a number of authors indicate that the presence of CMD is often underestimated in clinical practice. Despite irrefutable evidence of the relationship between endothelial dysfunction, impaired vasodilation of the coronary and systemic microvasculature, and HFpEF, the pathogenesis of CMD and its role in the initiation and progression of HFpEF, especially in the context of non-obstructive coronary artery disease (CAD), are being actively discussed [4, 5].

Intact endothelium of the arteries produces a large number of biologically active substances that maintain normal vasomotor activity [6]. An imbalance of vasodilation and vasoconstriction factors leads to suboptimal control of vascular tone and structure, characterized by disruption or loss of homeostatic mechanisms, which leads to elevated expression of adhesion molecules, increased oxidative stress, overproduction of prothrombotic and proinflammatory markers, increased proliferation of vascular smooth muscle cells, and increased vascular smooth muscle tone [6, 7]. Evidence accumulated over the past several decades has demonstrated that endothelial dysfunction and coronary vasomotor dysfunction play a crucial role in the pathogenesis of cardiovascular diseases [7]. However, the role of markers of endothelial dysfunction in the pathogenesis of CMD in patients with non-obstructive CAD and their role in stratifying the risk of HFpEF progression in this cohort of patients remain poorly studied.

The aim of this research was to study the potential of non-invasive biomarkers in the diagnosis of CMD and prediction of the course HFpEF in non-obstructive CAD.

MATERIALS AND METHODS

The study was approved by the Bioethics Committee at the Cardiology Research Institute of Tomsk NRMC (protocol No. 204 of 18.11.2020)) and was conducted in accordance with the principles of the Declaration of Helsinki and the guidelines for good clinical practice (GCP).

A 12-month observational study included 118 patients with HFpEF (62 [59; 64]%) without a previous history of CAD, complaining of chest pain, shortness of breath, or a combination of both. They were examined at the Cardiology Research Institute of Tomsk NRMC from 2019 to 2022. A detailed

description of the inclusion and exclusion criteria is presented in one of our previous works [8].

The presence and severity of coronary lesions were assessed by multislice spiral computed tomography (MSCT). The resulting scintigraphy images were processed on the specialized Xeleris 2 workstation (GEHealthcare, Israel), and the myocardial blood flow was assessed at rest (rest-MBF, ml / min / g) and during exercise during the administration of the stress agent ATP (stress-MBF, ml / min / g). Coronary flow reserve (CFR) was calculated according to the formula: MFR = stress-MBF / rest-MBF [9], and CMD was diagnosed at CFR ≤ 2 [10, 11].

Real-time 2D transthoracic echocardiography (2D speckle tracking) was performed on the Philips Affiniti 70 ultrasound system. LV diastolic dysfunction (peak E-wave velocity, the E/A ratio, lateral e', average E/e' ratio, left atrial volume index (LAVI), and peak tricuspid regurgitation velocity) and LV global longitudinal strain (GLS) were assessed [12].

Myocardial wall stress parameters, such as LV end-systolic elasticity (Es), arterial elastance (Ea), and LV myocardial wall stress in systole (MWSs) and diastole (MWSd), were calculated by formulas characterizing LV remodeling and presented in the work by T.A. Nechesova et al. [13].

The content of serum biomarkers (NT-proBNP; VEGF, and endothelin-1) was determined by the enzyme-linked immunosorbent assay (ELISA) using the Biomedica (Austria), Vector-best (Russia), and RayBio (USA) reagent kits, respectively (Fig. 1).

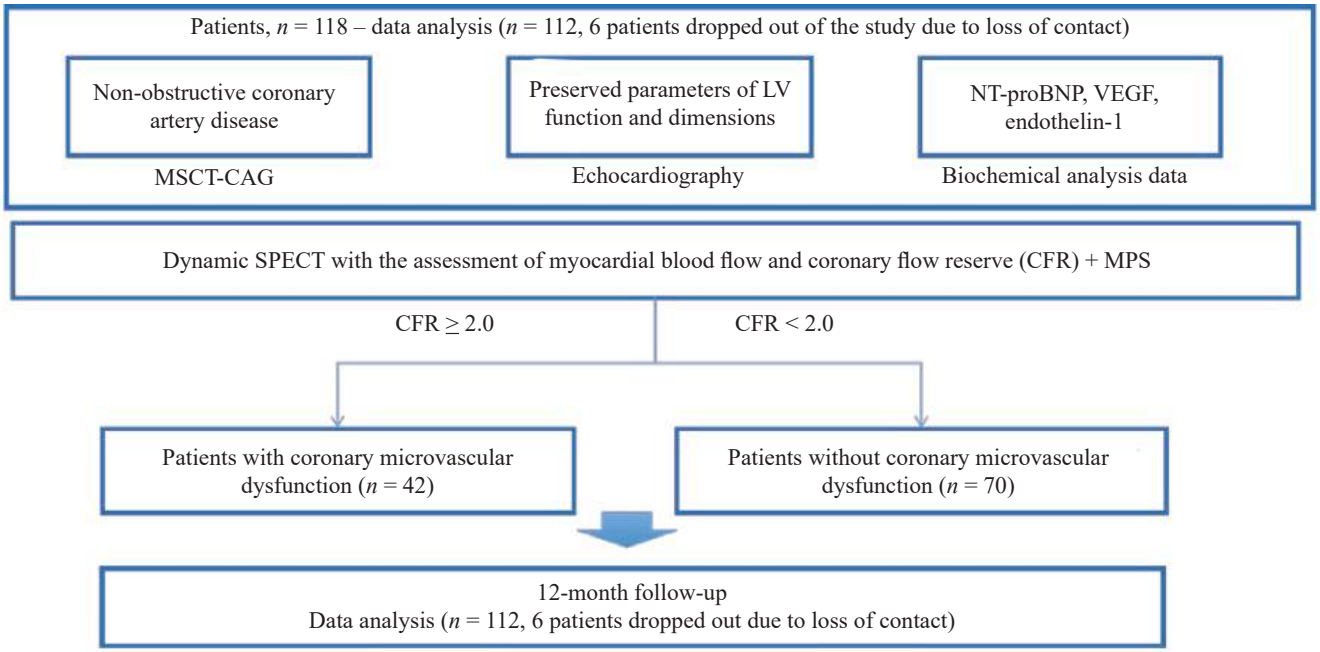


Fig. 1. Study design. NT-proBNP – NT-terminal pro-B-type natriuretic peptide, VEGF – vascular endothelial growth factor, MSCT – CAG – multislice spiral computed tomography – coronary angiography, MPS – myocardial perfusion scintigraphy

The results obtained were processed using the STATISTICA 10.0 and MedCalc 11.5.0.0 software packages. Quantitative variables were presented as the median and the interquartile range *Me* (Q_{25}; Q_{75}), qualitative variables were presented as absolute values (abs.) and percentage (%). When comparing quantitative variables in two independent groups, the Mann – Whitney test was used. When analyzing qualitative variables, contingency tables were analyzed using the Pearson's $\chi 2$ test. The univariate regression analysis with the calculation of odds ratio (OR) and 95% confidence interval (CI) was used to assess the influence of factors on the course of pathology. The multivariate regression analysis was used to identify independent predictors of adverse outcomes. To identify cut-off levels of biomarkers, the ROC analysis was used with the construction of ROC curves and calculation of area under the curve (AUC). The differences were considered statistically significant at $p \leq 0.05$.

RESULTS

Depending on the presence or absence of CMD, the patients were divided into 2 groups: group 1 included patients with CFR ≤ 2 (CMD+, n = 42), group 2 encompassed patients with CFR > 2 (CMD-, n = 70). Myocardial blood flow parameters differed significantly between the groups (Fig.2).

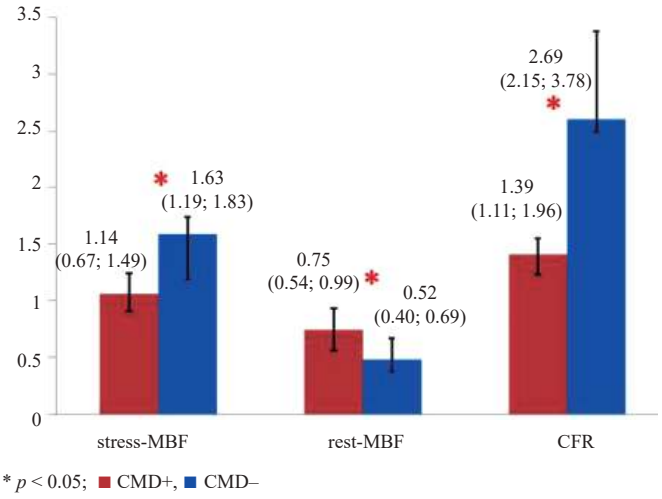


Fig. 2. Parameters of myocardial blood flow and coronary flow reserve depending on the presence of CMD. CFR – coronary flow reserve, stress-MBF – myocardial blood flow during exercise, rest-MBF – myocardial blood flow at rest.

Here and in Fig. 3, 4, p – level of statistical significance of the differences.

A history of type 2 diabetes mellitus (p = 0.003) and smoking status (p = 0.012) were significantly more often registered among patients with CMD. In this group of patients, 80.9% of those examined were diagnosed with HFpEF, while in group 2, there were significantly (p < 0.001) fewer patients with this phenotype of heart failure (34.3%). Other clinical and demographic parameters were comparable between the groups (Table 1).

The group of CMD+ patients was characterized by structural and functional changes corresponding to diastolic dysfunction in the context of non-obstructive CAD: a decrease in lateral e' values (by 35%; p = 0.009), a decrease in GLS (by 25.1%; p < 0.001) and an increase in the peak tricuspid regurgitation velocity (by 12%; p = 0.011), the E/e' ratio (by 21.4%; p = 0.041), and LAVI (by 51.2%; p = 0.038), respectively, compared to CMD- patients. Similar changes were noted in the parameters of systolic and diastolic myocardial wall stress, which were higher by 6.3 (p = 0.032) and 6.8% (p = 0.021), respectively, in the CMD+ group compared to the CMD- group. In patients of group 1, an increase in ventricular – arterial coupling (Ea/Es) by 25.9% (p = 0.032) was significantly more frequent compared to group 2, which characterizes decreased mechanical efficiency of the cardiovascular system in patients with CMD and non-obstructive CAD (Table 1).

Table 1

Characteristics of the patients at the time of inclusion in the study

Parameter	Group 1 (CMD +; n = 42)	Group 2 (CMD–; n = 70)	p
Age, years, *Me* (Q_{25}; Q_{75})	61.5 (55.0; 66.0)	62.0 (60.0; 67.0)	0.124
Men, n (%)	26 (61.9)	44 (62.8)	0.919
BMI, kg / m^2, *Me* (Q_{25}; Q_{75})	29.7 (27.6; 32.0)	30.1 (27.7; 34.1)	0.254
Type 2 diabetes mellitus, n (%)	11 (26.2)	5 (7.1)	0.003
COPD, n (%)	6 (14.3)	13 (18.6)	0.718
HFpEF, n (%)	34 (80.9)	24 (34.3)	<0.001
Smoking, n (%)	11 (26.2)	4 (5.7)	0.012
GFR (ml / min / 1.73 m^2), *Me* (Q_{25}; Q_{75})	76.8 (63.0; 81.0)	78.0 (64.0; 87.0)	0.476
Total cholesterol, mmol / l, *Me* (Q_{25}; Q_{75})	4.65 (3.67; 5.25)	4.34(3.54; 4.98)	0.932
LVEF, %, *Me* (Q_{25}; Q_{75})	62 (58.5; 65.0)	63 (61; 66)	0.183
ESD, mm, *Me* (Q_{25}; Q_{75})	40 (38; 43)	38.5 (36.5; 41.5)	0.524
EDD, mm, *Me* (Q_{25}; Q_{75})	51.0 (48.7; 53.0)	50.5 (47.5; 52.5)	0.307
Lateral e', cm / sec, *Me* (Q_{25}; Q_{75})	5.56 (4.78; 6.45)	8.56 (8.01; 9.14)	0.008
PTRV, m / sec, *Me* (Q_{25}; Q_{75})	2.98 (2.95; 3.01)	2.61 (2.3; 2.76)	0.009
E/e', *Me* (Q_{25}; Q_{75})	14 (13.5; 15.0)	11 (10; 12)	0.041
LAVI, ml / m^2, *Me* (Q_{25}; Q_{75})	38.3 (35.7; 51.1)	29.7 (27.5; 47.9)	0.038
GLS, %, *Me* (Q_{25}; Q_{75})	−14.9 (−13.1; −21.9)	−21.3 (−16.3; −22.8)	0.004

Table 1 (continued)

Parameter	Group 1 (CMD +; $n = 42$)	Group 2 (CMD–; $n = 70$)	p
MWSd, dyn / cm^2, *Me* (Q_{25}; Q_{75})	154.23 (140.11; 159.65)	140.13 (129.23; 151.54)	0.027
MWSs, dyn / cm^2, *Me* (Q_{25}; Q_{75})	172.18 (149.23; 192.34)	156.14 (134.23; 176.4)	0.022
Ea, mmHg./ ml, *Me* (Q_{25}; Q_{75})	0.61 (0.54; 0.89)	0.55 (0.52; 0.64)	0.028
Es, mmHg./ ml, *Me* (Q_{25}; Q_{75})	2.29 (1.67; 3.16)	2.78 (2.48; 3.09)	0.019
Ea / Es, *Me* (Q_{25}; Q_{75})	0.27 (0.23; 0.56)	0.20 (0.18; 0.45)	0.032

Note. BMI – body mass index, COPD – chronic obstructive pulmonary disease, HFpEF – heart failure with preserved ejection fraction, GFR – glomerular filtration rate, LVEF – left ventricular ejection fraction, ESD – left ventricular end-systolic dimension, EDD – left ventricular end-diastolic dimension, lateral e' – lateral mitral annulus velocity in early diastole, PTRV – peak tricuspid regurgitation velocity, E/e' – the ratio of transmitral E velocity to early diastolic mitral annular velocity, LAVI – left atrial volume index, GLS – global longitudinal strain, MWSd – myocardial wall stress in diastole, MWSs – myocardial wall stress in systole, Ea – arterial elastance, Es – end-systolic elastance, p – statistical significance of differences.

In patients in group 1, endothelin-1 levels were 1.9 times higher ($p = 0.012$), VEGF levels were 2.16 times higher ($p = 0.008$), and NT-proBNP levels were 2.6 times higher ($p = 0.004$) than in patients in group 2 (Fig. 3).

The ROC analysis revealed that VEGF overexpression ≥ 346.7 pg / ml (sensitivity 89.8%, specificity 72.4%; AUC = 0.756; $p = 0.002$) and endothelin-1 ≥ 6.9 pg / ml (sensitivity 84.6%, specificity 65.6%; AUC = 0.711; $p = 0.040$) had diagnostic value for identifying CMD in patients with non-obstructive CAD (Fig. 4).

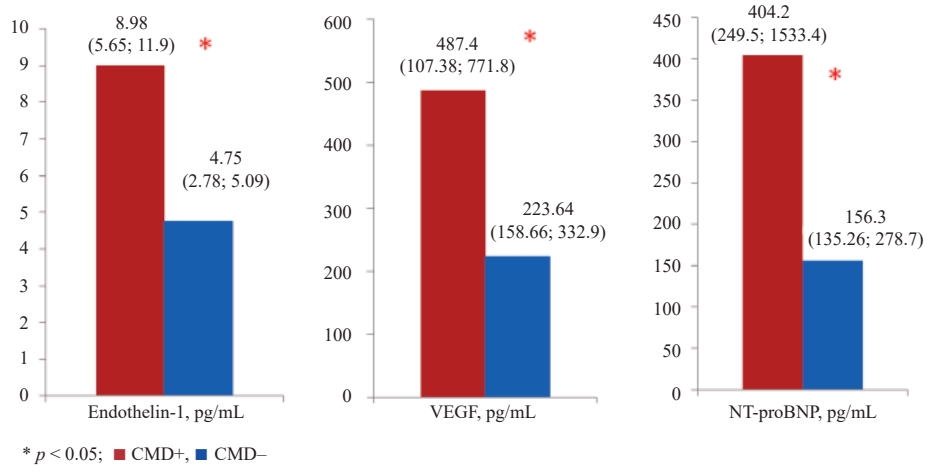
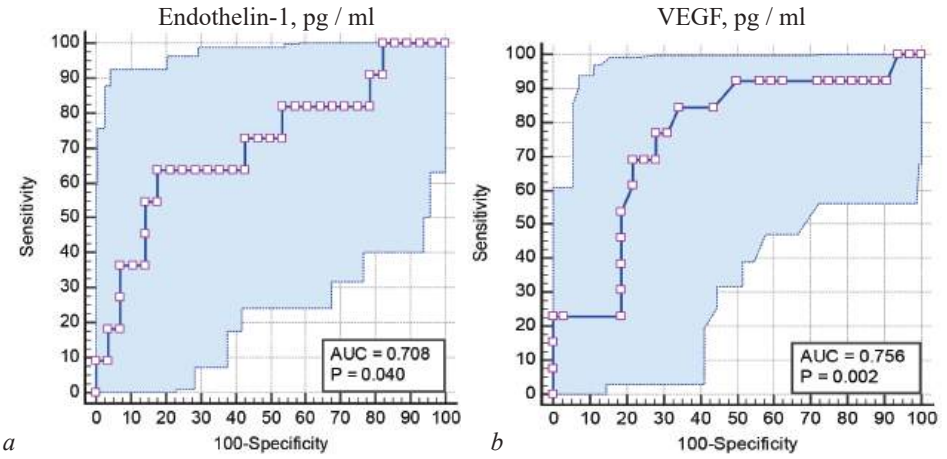


Fig. 3. Serum levels of the studied biomarkers in CMD+ or CMD- patients



a b

Fig. 4. Diagnostic value of endothelin-1 (*a*) and VEGF (*b*) levels in CMD (ROC analysis), AUC – area under the curve

During 12-month follow-up, 25 (22.3%) patients experienced adverse events (Fig. 5). The profile of adverse cardiovascular events was dominated by a complex parameter “HFpEF progression or intensification of diuretic therapy”. In one case, sudden cardiac death was registered

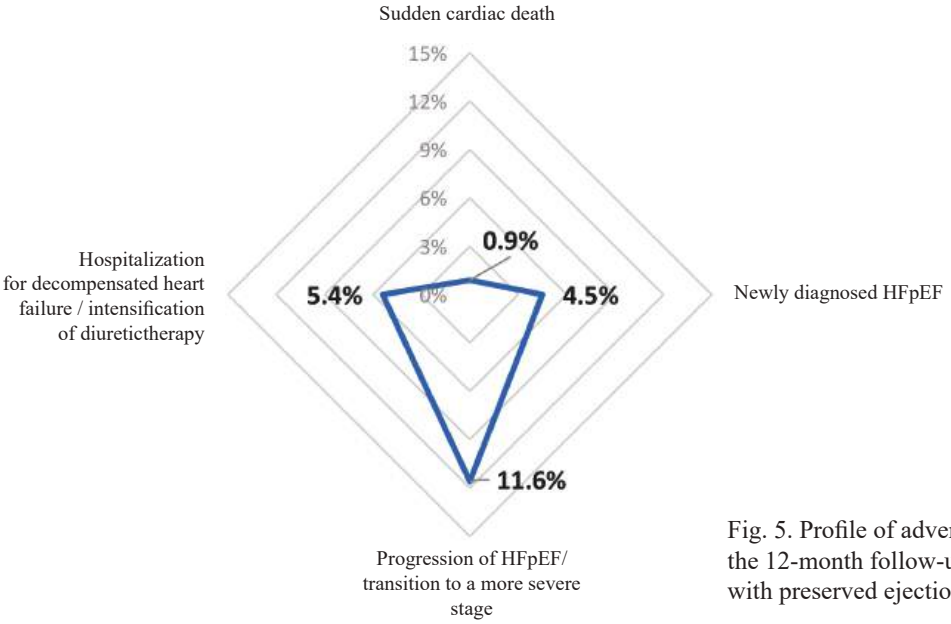


Fig. 5. Profile of adverse events registered during the 12-month follow-up. HFpEF – heart failure with preserved ejection fraction

The results of the univariate and multivariate regression models are presented in Table 2. Such factors as type 2 diabetes mellitus, CMD, smoking, overexpression of NT-proBNP ≥ 760.5 pg / ml, and endothelin-1 ≥ 4.9 pg / ml increased the risk of adverse cardiovascular events in patients with non-obstructive CAD by 1.9, 2.7, 2.3, 2, and 1.9 times, respectively. Assessing simultaneous influence of the predictors included in the analysis revealed that the factors associated with the development of adverse cardiovascular events were CMD and overexpression of NT-proBNP ≥ 760.5 pg / ml), and their combination increased the risk of HFpEF progression by more than 3 times (OR 3.18; 95% CI 2.76–7.98; $p < 0.001$). In the meantime, markers of endothelial dysfunction were not independent predictors.

Table 2

Analysis of the influence of risk factors for adverse cardiovascular events on outcomes in patients with non-obstructive coronary artery disease

Univariate regression analysis			
Factor	Odds ratio	95% CI	*p*
Type 2 diabetes mellitus	1.87	1.12–3.95	0.018
NT-proBNP (< 760.5 / ≥ 760.5 pg / ml)	1.98	1.09–3.98	0.028
GLS (>18≤/–18%)	1.98	0.99–5.98	0.002
Smoking	2.13	1.23–2.97	0.039
Coronary microvascular dysfunction	2.72	1.65–6.03	<0.001
Endothelin-1 (< 4.9 / ≥ 4.9 pg / ml)	1.95	0.98–5.87	0.002
VEGF (< 464.7 / ≥ 464.7 pg / ml)	2.65	1.76–9.12	0.001
Multivariate regression analysis			
Coronary microvascular dysfunction	2.42	1.26–5.85	<0.001
NT-proBNP (< 760.5 / ≥ 760.5 pg / ml)	1.33	1.08–3.19	0.025
CMD + NT-proBNP	3.18	2.76–7.98	<0.001

Note. NT-proBNP – N-terminal pro-B-type natriuretic peptide, GLS – global longitudinal strain, VEGF – vascular endothelial growth factor, CMD – coronary microvascular dysfunction, *p* – statistical significance of differences.

DISCUSSION

The present study found that CMD is closely associated with increased serum levels of a number of molecular biomarkers of endothelial activation and damage [14, 15]: endothelin-1 levels ≥ 6.9 pg / ml and VEGF ≥ 346.7 pg / ml can be used as non-invasive markers for diagnosing CMD. However, markers of endothelial dysfunction, according to our data, were not independent predictors of the HFpEF progression in patients with non-obstructive CAD within 12 months, which is likely associated with a more significant influence of nonspecific inflammatory factors, such as oxidative stress, profibrotic cytokines, and LV extracellular matrix remodeling, following specific changes in the structure of the sarcomeric protein titin [16, 17].

According to previously obtained data, CMD develops due to impaired endothelium-dependent and endothelium-independent vasodilation, as well as perivascular fibrosis. Moreover, CMD is one of the leading mechanisms for the development of HFpEF in patients with non-obstructive CAD in the context of increased ventricular – arterial coupling [16]. These processes lead to impaired myocardial perfusion, directing maladaptive responses of the body along the cardiovascular continuum [3–7]. Our data do not contradict the above concept. In particular, we showed that patients with CMD are diagnosed with more severe diastolic dysfunction and depressed mechanical efficiency of the cardiovascular system, manifested by an increase in Ea / Es and myocardial wall stress, associated with increased myocardial stiffness and increased LV pre- and afterload.

A recent study by S. Ohura-Kajitani et al. (2020) showed that both NO- and endothelium-dependent vasodilation were markedly impaired in patients with microvascular angina [14]. Another study found that CMD may precede epicardial dysfunction caused by oxidative stress and inflammation in early CAD [18]. The study by V. Lavin Plaza et al. (2020) showed that local inflammation in the vascular wall leads to endothelial dysfunction and accelerates the development and progression of atherosclerosis in peripheral arteries [19]. Therefore, when systemic endothelial dysfunction is detected, patients need to initiate early aggressive drug treatment aimed at restoring endothelial function and eliminating major risk factors.

Our study also found that patients with CMD had increased levels of serum biomarkers of endothelial activation and damage, which is likely associated with the influence of a number of risk factors (arterial hypertension, diabetes mellitus, hypercholesterolemia, etc.) on the development of functional and structural changes in the endothelium in the heart and the cardiovascular system as a whole. In particular, we found that increased serum levels of VEGF ≥ 346.7 pg / ml and endothelin-1 ≥ 6.9 pg / ml in patients with non-obstructive CAD can be considered as a marker of CMD presence.

Among the biomarkers of endothelial dysfunction, only asymmetric dimethylarginine (ADMA) and endothelin-1 have been studied the most in patients with CMD [20, 21]. Several investigators reported significantly higher plasma levels of ADMA and endothelin-1 in patients with CMD compared to controls and their association with adverse clinical outcomes [20, 22]. Our study also established an association of VEGF and endothelin-1 with adverse outcomes related to HFpEF progression, but these biomarkers were not independent predictors of risk stratification in the multivariate regression analysis. This is likely due to a relatively small patient sample and a small number of hard endpoints, such as readmissions and deaths.

LIMITATIONS OF THE STUDY

The main limitations of the study were a rather small sample size, heterogeneity of the sample, and short follow-up (12 months).

CONCLUSION

The results of this work, which stimulate further research in this area, can form the background for developing medical technologies for risk stratification in CMD and its early / preclinical diagnosis, which will determine the choice of personalized treatment strategy for this socially sensitive pathology and reduce the economic burden associated with its treatment costs.

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Authors' contribution

Kopeva K.V. – acquisition and interpretation of clinical data, statistical processing of the data, critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Maltseva A.N. – carrying out of scintigraphy, acquisition and interpretation of the data, compilation of the database, final approval of the manuscript for publication. Mochula A.V. – carrying out of scintigraphy, assessment of blood flow parameters, acquisition and interpretation of the data, compilation of the database, final approval of the manuscript for publication. Smorgon A.V. – carrying out of echocardiography, acquisition and interpretation of the data, compilation of the database, final approval of the manuscript for publication. Grakova E.V. – interpretation of the clinical data, drafting of the article, final approval of the manuscript for publication. Gusakova A.M. – determination of serum biomarker levels, acquisition and interpretation of the data, compilation of the database, final approval of the manuscript for publication. Kalyuzhin V.V. – review of literature, interpretation of the data, drafting of the article, final approval of the manuscript for publication. Zavadovsky K.V. – coordination of the research, drafting of the article, final approval of the manuscript for publication.

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