Kuzheleva E.A., Garganeeva A.A., Aleksandrenko V.A., Fedyunina V.A., Ogurkova O.N.
Research Institute for Cardiology, Tomsk National Research Medical Center,
Russian Academy of Sciences, Tomsk, Russia

Growth differentiation factor 15 associations with clinical features of chronic heart failure with midrange ejection fraction and preserved ejection fraction depending on the history of myocardial infarction

Aim	To analyze associations between levels of the inflammatory marker, growth differentiation factor 15 (GDF-15), and echocardiographic indexes in CHF patients with mid-range and preserved left ventricular ejection fraction (LV EF) depending on the history of myocardial infarction (MI).
Material and methods	This study included 34 CHF patients with preserved and mid-range LV EF after MI (group 1, n=19) and without a history of MI (group 2, n=15). Serum concentration of GDF-15 was measured with enzyme immunoassay (BioVendor, Czech Republic). Statistical analysis was performed with STATISTICA 10.0.
Results	Patients of the study groups were age-matched [62 (58;67) and 64 (60;70) years, p=0.2] but differed in the gender; group 1 consisted of men only (100%) whereas in group 2, the proportion of men was 53.3% (p=0.001). Median concentration of GDF-15 was 2385 (2274; 2632.5) and 1997 (1534; 2691) pg/ml in groups 1 and 2, respectively (p=0.09). Patients without MI showed a moderate negative correlation between LV EF and GDF-15 concentration (r= – 0.51, p=0.050) and a pronounced correlation between GDF-15 and LV stroke volume (r= –0.722, p=0.002). For patients after MI, a correlation between the level of GDF-15 and the degree of systolic dysfunction was not found (p>0.05).
Conclusion	Blood concentration of the inflammatory marker, GDF-15, correlates with LV EF and stroke volume in CHF patients with preserved or mid-range LV EF and without a history of MI while no such correlations were observed for patients with a history of MI.

Keywords	Chronic heart failure; growth differentiation factor 15; GDF-15; inflammation
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Corresponding author	Kuzheleva E.A. E-mail: snigireva1209@rambler.ru

In recent decades population-based studies have shown a sharp increase in the prevalence of chronic heart failure (CHF) worldwide [1–3]. CHF is associated with a significantly increased risk of mortality, leading to significant economic costs for the health-care budget associated with this pathology [2, 4]. Thus, the detailed study of pathogenesis mechanisms of heart failure (HF) is relevant since it is currently a very significant medical and social problem.

Special attention has been paid in recent years to the inflammatory theory of CHF pathogenesis. Chronic inflammation is one of the main mechanisms of the gradual depression of cardiac activity. This is clearly correlated with the pathogenesis, progression, severity, and prognosis of the disease [5]. Inflammatory biomarkers are increasingly used for the diagnosis and prognosis in HF. Growth differentiation factor 15 (GDF-15, GDF-15/MIC-1, growth differentiation factor 15/macrophage inhibitory cytokine 1) is one of such markers associated with inflammatory processes in the pathogenesis of CHF of any origin. It is a member of the superfamily of transforming growth factor-β (TGF-β) cytokines, first cloned as a macrophage-inhibiting cytokine 1 [6, 7]. GDF-15 is expressed as cardiomyocytes, adipocytes, macrophages, endothelial cells, and vascular smooth muscle cells in the case of tissue damage and inflammation [8–10].

Studies have shown that elevated levels of GDF-15 are associated with the development of endothelial dys-

function, atherosclerosis, myocardial infarction (MI), and HF. Increased GDF-15 levels are essentially indicative of the severity and poor prognosis of HF failure with reduced left ventricular ejection fraction (HFrEF), and HF with preserved ejection fraction (HFpEF) [10, 11]. There is evidence of correlation between increased levels of this inflammatory factor and echocardiographic parameters reflecting the diastolic dysfunction of the heart [12]. Moreover, one study revealed positive correlation between the concentration of this biomarker and CHF functional class, as well as the levels of brain natriuretic peptide in patients with HFpEF. Multivariate analysis showed that GDF-15 was a negative prognostic marker in these patients [13]. However, there is evidence that GDF-15 can inhibit apoptosis of cardiomyocytes by the activation of SMAD protein and provides a protective effect against hypertrophy and fibrosis [14]. However, the associations of this inflammatory marker with HF of different origins are still unknown.

Thus, the correlation of inflammatory agents, such as GDF-15, with the course CHF with the preserved systolic function of the heart depending on the presence or absence of a history of myocardial infarction (MI) remains insufficiently studied. Also the mechanisms of the causal relationship between the immune response and HF phenotype are still a matter of debate. For this reason further research in this area is required.

The objective of the study was to analyze the associations between the blood levels of inflammatory marker growth differentiation factor-15 (GDF-15), and the echocardiographic parameters in patients with CHF with mid-range and preserved left ventricular ejection fraction depending on a history of MI.

Material and methods

A pilot screening study was carried out with continuous inclusion of patients hospitalized in the Department of Myocardial Pathology, Institute of Cardiology, Tomsk National Research Medical Center, who fulfilled the relevant criteria. All patients signed the informed consent before the beginning of the study procedures. The study protocol was approved by the Ethics Committee of the Institute of Cardiology, Tomsk National Research Medical Center.

Inclusion criteria: CHF with LVEF ≥40% diagnosed under the current guidelines [15]; multivessel coronary disease (the presence of plaques occupying >70% of the lumen in LAD, LCX, RCA, or the presence of stenosis of LCA and RCA involvement).

Exclusion criteria: MI or progressing angina pectoris within three months before the inclusion; patient's refusal to participate in the study; severe respiratory insufficiency (exacerbation of chronic obstructive pulmonary disease, uncontrolled bronchial asthma); established cancer; and acute infection of exacerbation of chronic infectious disease.

The study included 34 patients (27 males and 7 females) of 62.5 (60; 68.3) years. All patients were examined in accordance with a single algorithm including: collection of complaints and medical history; clinical examination; calculation of body mass index; assessment of symptoms and signs of CHF; and 6-minute walk distance test. Clinical examination included electrocardiography, and echocardiogram using a Philips HD 15 ultrasound system [16]. Laboratory blood tests included complete blood count and differential white blood cell count, as well as a biochemical blood test (glucose, creatinine, lipid metabolism parameters, N-terminal pro-brain natriuretic peptide (NT-proBNP)). Glomerular filtration rate was calculated using the CKD EPI formula to evaluate renal function. If clinically indicated, coronary angiography was performed using a Siemens Axion Aptos angiographic complex within two months perior to inclusion.

Serum levels of GDF-15/MIC-1 were determined by enzyme-linked immunoassay (BioVendor, Czech Republic). The mean concentration of the study group was 2,370.3 (1,859.3; 2,851.4) pg/mL (Figure 1).

Patients were divided into two groups depending on a history of MI. Group 1 included patients with a history of myocardial infarction (n=19), while Group 2 comprised patients without a history of myocardial infarction (n=15).

Statistical processing of data was performed using STATISTICA 10.0. The quantitative data was described as the median and interquartile range in non-normal distribution verified using the Shapiro-Wilk test. The qualitative data is presented in terms of absolute and relative values (n (%)). The quantitative data in two independent samples was compared using the Mann-Whitney U-test. The statistical significance of differences between nominal signs was determined using contingency tables (the Pearson χ^2 test and the two-tailed Fisher exact test). The correlation analysis was performed using the Spearman correlation coefficient. The critical level of significance in the tests of statistical hypotheses was equal to 0.05 (p-value was the achieved level of significance).

Results

Patients included in the study groups were comparable in age but differed by sex. Group 1 was formed exclusively of male patients (100%), while Group 2 included similar numbers of male and female patients (53.3 and 46.7%, respectively).

Table 1 shows the main clinical and anamnestic characteristics of patients of the study groups.

Thus, the groups were comparable in terms of CHF functional classes, presence of arterial hypertension, atrial fibrillation, diabetes mellitus, glomerular filtration rate,

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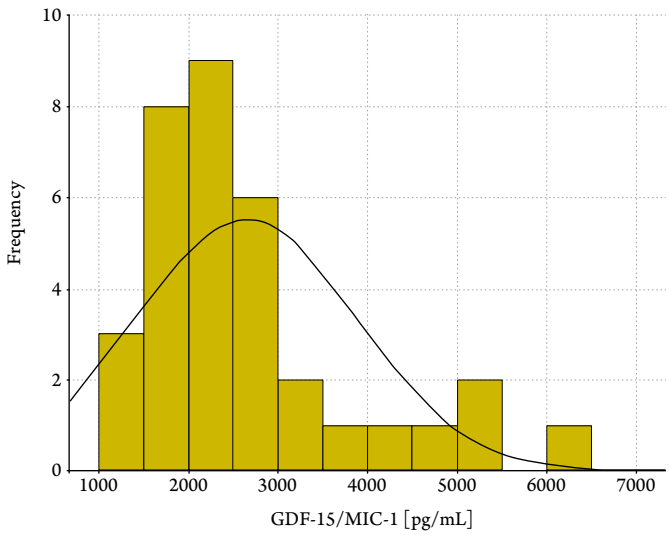
Figure 1. Distribution of GDF-15 levels in the study group of patients with CHF and multivessel coronary disease



and frequency of administering the main groups of drugs (Table 2). Each patient without a history of MI was overweight or presented obesity of varying degrees, unlike patients with a history of MI, half of whom presented normal body weight (p=0,006). However, statistical analysis detected no correlations between GDF-15 levels and body mass index (r= –0.1, p=0.5).

Table 3 shows the mean values of LVEF and other main echocardiographic indicators.

Thus, the groups did not differ in terms of LVEF. The values of other echocardiographic parameters were also comparable.

Analysis of general clinical laboratory parameters connected with the degree of inflammatory activity in the body and lipid profile did not reveal significant differences in the study groups, with the exception of a slightly higher monocyte count in patients with a history of MI (Table 4). NT-proBNP levels were comparable in the groups (p=0.2).

The mean level of GDF-15 was slightly elevated in patients with a history of MI: 2,385 (2,274; 2,632.5) pg/mL in Group; and 1,997 (1,534, 2,691) pg/mL in Group 2 (p=0.09) (Figure 2).

In the group of patients without a history MI, a moderate negative correlation was found between the levels of inflammatory marker GDF-15 and LVEF (r=–0.51, p=0.050), and a strong correlation between this indicator and LV stroke volume (r=–0.722, p=0.002). However, in patients with a history of MI no correlation between GDF-15 levels and the degree of LV systolic dysfunction (r=0.275, p=0.3) and the value of stroke volume (r=0.156, p=0.5) was detected.

Table 1. Clinical and anamnestic characteristics of patients in the study groups

Parameter	Patients with a history of MI (n = 19)	Patients without a history of MI (n = 15)	p
Age, years	62 (58; 67)	64 (60; 70)	0.2
Typical angina pain, n (%)	19 (100)	14 (93.3)	0.4
History of several MIs, n (%)	2 (10.5)	-	–
Time after the last MI, months	36 (8.5;108)	-	–
Problems with heart, n (%)	5 (26.3)	6 (40)	0.5
CHF FC, n (%) • I • II • III	 1 (5.3) 14 (73.7) 4 (21)	 2 (13.3) 9 (60) 4 (26.7)	0.9
6-minute walk distance, m	330 (302; 391)	345 (280; 401)	0.6
Dyspnea, n (%)	19 (100)	15 (100)	0.99
Weakness/fatigue, n (%)	12 (63)	8 (53)	0.6
Leg edema, n (%)	1 (5)	1 (6.7)	0.7
Arterial hypertension, n (%)	19 (100)	15 (100)	0.47
Diabetes mellitus, n (%)	7 (36.8)	4 (26.7)	0.55
Normal weight, n (%)	7 (46.7)	0	0.006
Body mass index ≥25 kg/m^2	12 (53.3)	15 (100)	0.006
Body mass index, kg/m^2	26 (24.5; 29.5)	32.6 (27.2; 34.5)	0.005
Atrial fibrillation (any form), n (%)	3 (15.8)	4 (26.7)	0.67
GFR (CKD EPI), mL/min/1.73 m^2	70 (59.25; 75.5)	65.5 (59.5; 76.25)	0.6
HFmrEF, n (%)	2 (10.5)	2 (13.3)	0.8
HFpEF, n (%)	17 (89.5)	13 (86.7)	0.8

CHF, chronic heart failure; FC, functional class; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction; Me (Q25; Q75), median and interquartile range; p, level of significance.

Figure 2. GDF-15 levels in the groups with (1) and without (0) a history of MI

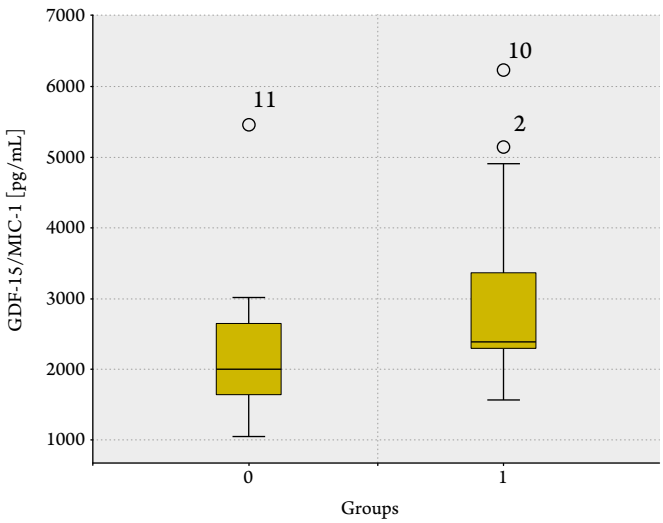


Table 2. Drug therapy of CHF before hospitalization

Group of drugs	Patients with a history of MI (n=19)	Patients without a history of MI (n=15)	p
Beta-blockers, n (%)	18 (94.7)	11 (73)	0.1
ACE inhibitors, n (%)	10 (52.6)	7 (47)	0.5
ARBs, n (%)	5 (26.3)	6 (40)	0.4
MCRA, n (%)	2 (10.5)	0	0.3
Diuretics, n (%)	7 (36.8)	10 (66.7)	0.08
Statins, n (%)	16 (84.2)	9 (60)	0.1
Antiplatelet drugs, n (%)	19 (100)	15 (100)	0.99

BBs, beta-blockers; ACE, angiotensin converting enzyme; ARBs, aldosterone receptor blockers; MCRA, mineralocorticoid receptor antagonists; p, level of significance.

Discussion

According to the results obtained, GDF-15 levels in the study group were high: 2,370.3 (1,859.3; 2,851.4) pg/mL. The resulting value was higher than the marker levels in the cohort of patients with acute MI [17, 18], with a median GDF-15 level of ≤1500 pg/mL. However, examination of patients with postinfarction cardiosclerosis established a progressive increase in GDF-15 concentration over time after MI, and as CHF developed and progressed [6, 19], which is consistent with our findings.

All patients without a history of MI were overweight or presented obesity, unlike patients with a history of MI. This factor could in theory influence the GDF-15 levels in the treatment groups [20]. At the same time, statistical

Table 3. Main echocardiographic parameters of patients with or without a history of MI

Parameter	Patients with a history of MI (n=19)	Patients without a history of MI (n=15)	p
LVEF, %	63 (60;65)	64 (60;65.5)	0.6
LVMI, g/m²	92 (88;98)	92 (88;101)	0.9
LV systolic volume, mL	70 (68;76)	67 (64;72)	0.08
LVEDV, mL	116 (105;130)	109 (103;118)	0.2
LVESV, mL	43 (37;48)	41 (37;44)	0.3
LVESI , mL/m²	21.5 (20.7;24.1)	20.7 (19.1; 24.8)	0.4
LVEDI , mL/m²	59.5 (55;63.6)	58.1 (55;60.8)	0.4
LVESD, mm	33 (31;36)	32 (31;34.5)	0.3
LVEDD, mm	50 (49;53)	50 (49;51)	0.5
LA volume index, mL/m²	38 (34.1;49.5)	37.1 (33.9;47.5)	0.9
E, sm/sec	74.5 (62.2;87)	69.5 (59;83.5)	0.3
E/A	0.96 (0.9;1.52)	0.92 (0.86;1.4)	0.5
E/e'	12.5 (8.6;15.1)	9.8 (7.8;14.3)	0.2

MI, myocardial infarction; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEDI, left ventricular end-diastolic index; LVESI, left ventricular end-systolic index; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LA, left atrium; Me (Q25; Q75), median and interquartile range; p, level of significance.

Table 4. Main laboratory findings

Parameter	Patients with a history of MI (n=19)	Patients without a history of MI (n=15)	p
GDF-15, pg/mL	2385 (2274; 2632.5)	1997 (1534; 2691)	0.09
NT-proBNP, pg/mL	352 (210;418)	285 (191;398)	0.2
WBCs, 10^9/L	8.1 (6.9;10.2)	7 (6.2;9.1)	0.15
Monocytes, 10^9/L	0.74 (0.64;1.03)	0.66 (0.46;0.74)	0.03
Neutrophils, 10^9/L	3.97 (3.13;6.3)	3.38 (2.65;4.4)	0.14
Lymphocytes, 10^9/L	2.69 (2.47;3.73)	2.7 (2.36;3.9)	0.78
Platelets, 10^9/L	213 (197;245)	228 (193.5;260)	0.9
Fibrinogen, g/L	3.57 (3.06;3.97)	3.37 (3.06;3.68)	0.6
Total cholesterol, mmol/L	4.19 (3.53;5.54)	5.1 (3.8;5.89)	0.4
Low -ensity lipoprotein cholesterol, mmol/L	3.38 (2.3;3.8)	3.12 (1.57;4.17)	0.9
High-density lipoprotein cholesterol, mmol/L	1.12 (0.98;1.53)	1.11 (0.98;1.22)	0.6
Triglycerides, mmol/L	1.5 (1.03;2.35)	1.98 (1.22;2.38)	0.3

MI, myocardial infarction; GDF-15, growth differentiation factor 15. NT-proBNP, N-terminal pro-brain natriuretic peptide; Me (Q25; Q75), median and interquartile range; p, level of significance.

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analysis detected no correlations between the levels of the biomarker of interest and body mass index.

However, it remains unclear for what CHF phenotype is GDF-15 the most informative. According to certain data, increased GDF-15 is typical of patients with a more severe clinical pattern of CHF, while it increases as LVEF decreases [21, 22]. According to other data, GDF-15 is better correlated with LV diastolic dysfunction than with NT-proBNP. This is the case especially in obese patients [20], and is also superior to NT-proBNP in terms of identifying patients with HFpEF and HFmrEF with a worse prognosis [11].

In our study, correlations between GDF-15 levels and echocardiographic parameters of the systolic function of the heart (LVEF, stroke volume) were identified in the group of patients without a history of MI. Thus, the absence of a direct correlation between the systolic function of the heart and GDF-15 levels in patients with a history of MI may in part be caused by a wide range of post-infarction remodeling processes, including fibrotic scarring and proliferation [23, 24].

The associations of GDF-15 with LVEF and LV stroke volume discovered in patients without a history of MI are consistent with studies confirming the potential of this inflammatory component being considered a marker of HFrEF progression [12].

Thus, the established differences in the correlations between GDF-15 and the development of HF dependent on a history of MI form an important basis for the further study of the development of CHF and its progression mechanisms. Given that the diagnosis, treatment, and prognosis of HFrEF still remain controversial and unresolved issues in scientific and practical cardiology, further research in this area is both necessary and relevant.

Limitations

The main limitation of the study was the small number of patients in the study groups. Given that GDF-15 levels depend on many factors, including body mass index, the lack of standardization in the study groups in terms of this parameter was also a limitation to our study.

Conclusion

The blood levels of inflammatory marker GDF-15 correlate with left ventricular ejection fraction, and stroke volume in patients with chronic heart failure with preserved left ventricular ejection fraction and mid-range left ventricular ejection fraction. Similar associations were not identified in patients with a history of myocardial infarction.

No conflict of interest is reported.

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