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THE INFLUENCE OF ENDOTHELIAL DYSFUNCTION ON THE FORMATION OF CARDIOVASCULAR RISK IN CHRONIC HEART FAILURE

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Abstract. — to assess the influence of endothelial dysfunction on the formation of cardiovascular risk in patients with chronic heart failure. The study included 120 patients with chronic heart failure of functional class II–III. Clinical manifestations of the disease, cardiovascular risk factors, lipid profile, high-sensitivity C-reactive protein level, NT-proBNP, echocardiographic data, the six-minute walk test, and indicators of endothelium-dependent vasodilation were evaluated.

It was established that endothelial dysfunction was detected in 61.7% of patients and was associated with a higher frequency of arterial hypertension, ischemic heart disease, type 2 diabetes mellitus, obesity, dyslipidemia, inflammatory activity, and reduced exercise tolerance. According to multivariate analysis, endothelial dysfunction remained an independent factor of high cardiovascular risk.

Keywords: chronic heart failure, endothelial dysfunction, cardiovascular risk, inflammation, dyslipidemia, oxidative stress, prognosis.

INTRODUCTION

Chronic heart failure (CHF) remains one of the most urgent problems of modern cardiology, as it is accompanied by a high frequency of hospitalizations, reduced quality of life, and an unfavorable prognosis. In current international guidelines, CHF is considered a complex clinical syndrome that requires early diagnosis, risk stratification, active control of comorbid conditions, and the use of therapy that affects not only symptoms but also long-term outcomes [1, 2].

The modern understanding of CHF goes beyond isolated impairment of the heart's pumping function. Disease progression is associated with chronic neurohumoral activation, systemic inflammation, oxidative stress, microcirculatory disorders, and remodeling of the myocardium and vascular wall [2, 8]. Endothelial dysfunction occupies an important place among these mechanisms.

The endothelium is an active regulator of vascular homeostasis. It participates in the control of vascular tone, hemostasis, inflammatory response, leukocyte adhesion, and vascular remodeling processes. Under normal conditions, the endothelium maintains a balance between vasodilation and vasoconstriction, as well as between antithrombotic and prothrombotic mechanisms. Disruption of this balance leads to vascular damage and increased cardiovascular risk [4, 5].

of the vascular wall, reduces platelet aggregation, decreases leukocyte adhesion, and has an anti-inflammatory effect. In CHF, nitric oxide bioavailability decreases due to oxidative stress, inflammation, and impaired endothelial NO synthase activity [6, 7]. This leads to increased peripheral vascular resistance, impaired tissue perfusion, and reduced exercise tolerance.

Endothelial dysfunction in CHF has a dual significance. On the one hand, it is a consequence of hemodynamic overload, neurohumoral activation, and inflammatory vascular injury. On the other hand, it itself supports the progression of heart failure by worsening vasodilation, increasing afterload, and impairing coronary microcirculation [4, 6].

Cardiovascular risk in CHF is formed under the influence of age, arterial hypertension, ischemic heart disease, diabetes mellitus, dyslipidemia, obesity, chronic kidney disease, and inflammatory activity. Endothelial dysfunction reflects the cumulative impact of these factors and may be considered an integral marker of vascular risk [5, 11]. Dyslipidemia, hyperglycemia,

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and arterial hypertension damage the endothelium, activate inflammation, enhance oxidative stress, and contribute to the progression of atherosclerosis [10, 12].

Endothelial dysfunction is of particular importance in patients with CHF with preserved or mildly reduced ejection fraction. According to the concept proposed by Paulus and Tschöpe, comorbid conditions induce systemic inflammation and coronary microvascular endothelial dysfunction, which contributes to diastolic dysfunction and the progression of heart failure [8].

Thus, the study of endothelial dysfunction in CHF has important scientific and practical significance. Assessment of endothelial function may improve risk stratification, identify patients with an unfavorable prognosis, and contribute to the individualization of therapeutic and preventive measures.

Materials and methods. The study was conducted as a clinical observational study aimed at assessing the relationship between endothelial dysfunction and cardiovascular risk in patients with CHF. The methodological basis of the study was developed taking into account the current AHA/ACC/HFSA and ESC guidelines for the diagnosis and management of patients with heart failure [1, 2, 3].

The study included 120 patients with CHF of functional class II–III. The diagnosis was established on the basis of complaints, medical history, physical examination, electrocardiography, echocardiography, and laboratory parameters. Inclusion criteria were age over 40 years, confirmed CHF, stable clinical condition, and consent to participate in the study.

Exclusion criteria included acute myocardial infarction or stroke within the previous three months, active infections, severe renal failure, oncological diseases, active autoimmune processes, and decompensated endocrine disorders. The exclusion of these conditions was necessary because they may independently influence endothelial function, inflammatory marker levels, and cardiovascular risk [4, 9, 10].

In all patients, disease duration, frequency of hospitalizations, exercise tolerance, current therapy, and comorbid conditions were assessed. Special attention was paid to arterial hypertension, ischemic heart disease, type 2 diabetes mellitus, dyslipidemia, obesity, smoking, family history, and low physical activity, since these factors are important determinants of CHF progression and endothelial damage [1, 2, 5, 11].

Physical examination included measurement of blood pressure, heart rate, body weight, height, body mass index, and waist circumference. Functional status was assessed using the six-minute walk test, which reflects exercise tolerance and the degree of functional limitation in CHF [21, 22,23,24].

Laboratory examination included complete blood count, glucose, creatinine, estimated glomerular filtration rate, total cholesterol, low-density and high-density lipoproteins, triglycerides, high-sensitivity C-reactive protein, and NT-proBNP. Natriuretic peptides were used as markers of myocardial stress and CHF prognosis [1, 2]. The lipid profile was assessed to identify atherogenic dyslipidemia, while high-sensitivity C-reactive protein was used to assess systemic inflammation [9, 10, 12].

Instrumental methods included electrocardiography and echocardiography. Echocardiography assessed left ventricular ejection fraction, chamber dimensions, myocardial hypertrophy, diastolic function, valvular status, and signs of pulmonary hypertension. Echocardiography is a basic method for confirming structural and functional changes of the heart in CHF [11,12,13].

Endothelial function was assessed by endothelium-dependent vasodilation. A decrease in this indicator was considered a manifestation of endothelial dysfunction, since the ability of the artery to dilate reflects nitric oxide bioavailability and the functional state of the endothelial layer [14,15,16,17]. Depending on the results, patients were divided into two groups: those with relatively preserved endothelial function and those with endothelial dysfunction.

Statistical analysis included descriptive statistics, comparative analysis, correlation analysis, and multivariate regression. Quantitative indicators are presented as mean and standard deviation,

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and qualitative indicators as absolute numbers and percentages[18,19,20]. Differences were considered statistically significant at $p<0.05$.

Results. The study included 120 patients with CHF of functional class II–III. The mean age was 62.8±8.7 years. There were 68 men (56.7%) and 52 women (43.3%). Functional class II CHF was detected in 71 patients (59.2%), while functional class III CHF was detected in 49 patients (40.8%). The mean duration of the disease was 6.4±3.1 years.

According to the assessment of endothelium-dependent vasodilation, the patients were divided into two groups. The first group included 46 patients (38.3%) with relatively preserved endothelial function, while the second group included 74 patients (61.7%) with endothelial dysfunction. The high frequency of endothelial dysfunction in patients with CHF is consistent with data on the role of oxidative stress, inflammation, and vascular remodeling in heart failure.

Patients with endothelial dysfunction were older: 64.1±8.5 years versus 60.7±8.4 years in the comparison group ($p=0.034$). This confirms the contribution of age to vascular aging, reduced nitric oxide bioavailability, and increased vascular stiffness.

The frequency of cardiovascular risk factors was higher in patients with endothelial dysfunction. Arterial hypertension was detected in 85.1% versus 67.4% of patients ($p=0.021$), ischemic heart disease in 75.7% versus 58.7% ($p=0.046$), type 2 diabetes mellitus in 37.8% versus 19.6% ($p=0.032$), and obesity in 45.9% versus 26.1% ($p=0.029$). These data confirm the role of endothelial dysfunction as an integral indicator of vascular risk.

Clinical manifestations of CHF were also more pronounced in the endothelial dysfunction group. Dyspnea during moderate physical activity was observed in 91.9% versus 73.9% of patients ($p=0.008$), fatigue in 87.8% versus 69.6% ($p=0.014$), peripheral edema in 52.7% versus 32.6% ($p=0.031$), and palpitations in 56.8% versus 37.0% ($p=0.036$). This indicates an association between endothelial damage and a more severe clinical course of CHF.

According to the six-minute walk test, the mean distance in patients with endothelial dysfunction was 284.6±62.3 m, whereas in patients with relatively preserved endothelial function it was 341.8±58.7 m ($p<0.001$). The reduced distance may reflect impaired peripheral vasodilation, microcirculation, and oxygen delivery to skeletal muscles.

Laboratory analysis revealed a more unfavorable lipid profile in patients with endothelial dysfunction. Total cholesterol was 6.12±0.84 mmol/L versus 5.48±0.76 mmol/L ($p<0.001$), low-density lipoproteins were 3.82±0.71 mmol/L versus 3.21±0.65 mmol/L ($p<0.001$), and triglycerides were 2.14±0.58 mmol/L versus 1.72±0.49 mmol/L ($p=0.002$). High-density lipoproteins were lower: 1.02±0.21 mmol/L versus 1.18±0.24 mmol/L ($p=0.001$). These changes confirm the relationship between atherogenic dyslipidemia and endothelial damage.

The level of high-sensitivity C-reactive protein was higher in patients with endothelial dysfunction: 6.8±2.4 mg/L versus 3.9±1.7 mg/L ($p<0.001$). This indicates the role of systemic inflammation in endothelial injury and the progression of vascular dysfunction [9, 10, 12]. The NT-proBNP level was also higher: 1286±514 pg/mL versus 876±392 pg/mL ($p<0.001$), indicating greater myocardial stress.

Renal function was worse in patients with endothelial dysfunction: estimated glomerular filtration rate was 62.4±14.8 mL/min/1.73 m^2 versus 71.6±13.9 mL/min/1.73 m^2 ($p=0.001$). This may reflect the systemic nature of vascular damage and microcirculatory disorders.

According to echocardiography, patients with endothelial dysfunction had a lower left ventricular ejection fraction: 42.6±7.8% versus 47.9±8.1% ($p=0.001$). Left atrial enlargement was detected in 64.9% versus 41.3% of patients ($p=0.011$), left ventricular hypertrophy in 68.9% versus 47.8% ($p=0.021$), and diastolic dysfunction in 79.7% versus 56.5% ($p=0.007$). These data confirm the association between endothelial damage and cardiac remodeling.

Correlation analysis revealed an inverse relationship between endothelium-dependent vasodilation and high-sensitivity C-reactive protein ($r=-0.46$; $p<0.001$), low-density lipoproteins ($r=-0.39$; $p<0.001$), triglycerides ($r=-0.31$; $p=0.004$), and NT-proBNP ($r=-0.42$; $p<0.001$). A positive correlation was established with the six-minute walk distance ($r=0.44$; $p<0.001$) and left

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ventricular ejection fraction (r=0.36; p=0.002). This confirms the relationship of endothelial function with inflammation, lipid metabolism, CHF severity, and exercise tolerance.

Multivariate regression analysis showed that endothelial dysfunction remained an independent factor of high cardiovascular risk: odds ratio 2.84; 95% confidence interval 1.34–6.02; p=0.006. Independent predictors also included NT-proBNP, type 2 diabetes mellitus, and high-sensitivity C-reactive protein. High overall cardiovascular risk was detected in 73.0% of patients with endothelial dysfunction and in 41.3% of patients in the comparison group (p<0.001).

Discussion. The obtained results confirm that endothelial dysfunction is a significant pathogenetic factor in the formation of cardiovascular risk in patients with CHF. In our study, it was detected in 61.7% of patients, indicating a high prevalence of vascular damage in this disease. This finding is consistent with the current concept of CHF as a multisystem syndrome involving neurohumoral activation, inflammation, oxidative stress, and vascular wall remodeling.

The association of endothelial dysfunction with age, arterial hypertension, ischemic heart disease, diabetes mellitus, and obesity confirms its role as an integral marker of vascular risk. In patients with endothelial dysfunction, arterial hypertension was present in 85.1%, ischemic heart disease in 75.7%, diabetes mellitus in 37.8%, and obesity in 45.9%. These differences were statistically significant and are consistent with data indicating that endothelial function reflects the cumulative effect of traditional risk factors on the vascular wall.

Arterial hypertension contributes to mechanical injury of the endothelium, reduced nitric oxide production, increased vascular stiffness, and increased afterload on the left ventricle. In patients with CHF, this accelerates myocardial remodeling and worsens the clinical prognosis. Therefore, current guidelines emphasize the need for strict blood pressure control in patients with heart failure.

Metabolic disorders also play an important role in the formation of endothelial dysfunction. In our study, patients with impaired endothelial function had higher levels of total cholesterol, low-density lipoproteins, and triglycerides, as well as lower levels of high-density lipoproteins. Atherogenic dyslipidemia damages the endothelium, activates inflammation in the vascular wall, and contributes to the progression of atherosclerosis. Diabetes mellitus enhances these processes through hyperglycemia, insulin resistance, oxidative stress, and chronic inflammation.

The identified association between endothelial dysfunction and systemic inflammation is of particular importance. The level of high-sensitivity C-reactive protein was significantly higher in patients with impaired endothelial function, and correlation analysis showed an inverse relationship between endothelium-dependent vasodilation and this marker (r=-0.46; p<0.001). This confirms that inflammation contributes to reduced nitric oxide bioavailability, endothelial cell activation, and progression of vascular damage.

Oxidative stress is one of the central mechanisms explaining the obtained results. Excessive formation of reactive oxygen species leads to inactivation of nitric oxide, damage to cell membranes, and activation of inflammatory pathways. Landmesser et al. demonstrated a close relationship between vascular oxidative stress and endothelial dysfunction in patients with CHF. In our study, the combination of inflammation, dyslipidemia, and reduced endothelium-dependent vasodilation also indicates the involvement of an oxidative-inflammatory mechanism.

The clinical significance of endothelial dysfunction is confirmed by more pronounced CHF symptoms and reduced exercise tolerance. Patients with endothelial dysfunction more often had dyspnea, fatigue, edema, and palpitations. The six-minute walk distance was significantly lower: 284.6±62.3 m versus 341.8±58.7 m (p<0.001). The positive correlation between endothelium-dependent vasodilation and walking distance (r=0.44; p<0.001) indicates the role of peripheral microcirculation in the formation of functional limitations in CHF.

Echocardiographic data show that endothelial dysfunction is associated with unfavorable cardiac remodeling. Patients with endothelial dysfunction had lower left ventricular ejection fraction and more frequently demonstrated left atrial enlargement, left ventricular hypertrophy,

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and diastolic dysfunction. The relationship with diastolic disorders is especially important, since microvascular inflammation and endothelial dysfunction are considered key mechanisms in the development of CHF with preserved ejection fraction [8].

Increased NT-proBNP levels in patients with endothelial dysfunction confirm the relationship between vascular damage and myocardial stress severity. The NT-proBNP level was 1286±514 pg/mL versus 876±392 pg/mL ($p<0.001$), and its inverse correlation with endothelium-dependent vasodilation ($r=-0.42$; $p<0.001$) indicates an interaction between hemodynamic overload and vascular dysfunction.

The most important finding is that endothelial dysfunction remained an independent factor of high cardiovascular risk according to multivariate analysis: odds ratio 2.84; 95% confidence interval 1.34–6.02; $p=0.006$. This confirms its independent clinical and prognostic significance and is consistent with data showing that endothelial function may be used as an indicator of an unfavorable vascular prognosis.

The practical significance of the study is that assessment of endothelial function may complement traditional methods of risk stratification in CHF. Functional class, ejection fraction, NT-proBNP, and comorbidity remain the basis of clinical assessment; however, they do not always fully reflect the condition of the vascular system. Assessment of endothelium-dependent vasodilation makes it possible to identify patients with pronounced vascular damage, inflammatory activity, and high metabolic risk.

From a clinical perspective, detection of endothelial dysfunction requires more active correction of modifiable risk factors. Blood pressure control, correction of dyslipidemia, optimization of glycemia, weight reduction, smoking cessation, physical activity, and modern basic therapy for CHF may contribute to improvement of vascular function and reduction of complication risk.

A limitation of the study is its clinical observational design, which allows associations to be established but does not prove a causal relationship. In addition, the sample of 120 patients requires further confirmation in larger populations. A promising direction is the dynamic assessment of endothelial function during therapy and the study of its relationship with the frequency of decompensation, hospitalizations, and cardiovascular mortality.

Thus, endothelial dysfunction is a significant clinical, pathogenetic, and prognostic component of CHF. It is associated with traditional risk factors, inflammation, dyslipidemia, reduced exercise tolerance, elevated NT-proBNP, impaired renal function, and unfavorable echocardiographic changes. Its assessment may be used to improve risk stratification and individualize therapeutic and preventive measures.

Conclusion. Endothelial dysfunction plays an important role in the formation of cardiovascular risk in patients with chronic heart failure. It is associated with more pronounced clinical manifestations of the disease, reduced exercise tolerance, increased inflammatory activity, lipid metabolism disorders, and signs of structural and functional cardiac remodeling.

Assessment of endothelial function may be considered an additional diagnostic and prognostic tool in the comprehensive examination of patients with chronic heart failure. Detection of endothelial dysfunction makes it possible to identify a high cardiovascular risk group in a timely manner and intensify therapeutic and preventive measures.

A comprehensive approach to the management of such patients should include active correction of arterial hypertension, dyslipidemia, diabetes mellitus, obesity, inflammatory activity, and other modifiable risk factors. This may contribute to improved prognosis, reduced frequency of decompensation, and improved quality of life.

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