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A pathophysiological assessment of structural myocardial damage and hemodynamic overload

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Modern cardiology is actively searching for effective approaches to the early diagnosis and prediction of heart failure, which remains a leading cause of disability and mortality. Alongside established markers of hemodynamic stress, such as B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide (NT-proBNP), interest is growing in myoglobin as a potential indicator of structural myocardial damage. The aim of this study was to assess the relationship between plasma myoglobin and NT-proBNP levels in patients with chronic heart failure (CHF) of various etiologies and to substantiate the concept of an integrated pathophysiological continuum linking myocardial damage and hemodynamic stress. This prospective, single-center, cross-sectional observational study included 138 participants, of whom 123 had CHF of various etiologies and 15 served as controls. Patients were stratified according to CHF etiology (valvular and non-valvular) and the presence of thromboembolic complications. Plasma myoglobin and NT-proBNP levels were measured by ELISA. Statistical analysis included nonparametric tests and correlation analysis. Patients with CHF had significantly higher myoglobin and NT-proBNP levels than controls. Myoglobin concentrations were highest in patients with non-valvular CHF, showing a 2.6-fold increase compared with controls, indicating persistent structural and metabolic myocardial stress. NT-proBNP levels were significantly elevated in all CHF groups, with the highest values observed in patients with combined valvular pathology. A significant positive correlation was found between plasma myoglobin and NT-proBNP levels (r = 0.397). ROC analysis demonstrated a statistically significant association between myoglobin levels and signs of heart failure defined by NT-proBNP concentrations >900 pg/ml (0.687; 95% CI: 0.581-0.792; P = 0.001), indicating a moderate discriminatory ability of the marker. The combined assessment of myoglobin and NT-proBNP reflects complementary aspects of CHF pathophysiology by integrating structural myocardial damage and hemodynamic stress. This two-marker approach represents a parsimonious yet pathogenetically grounded model that may improve risk stratification and facilitate the development of personalized diagnostic strategies in patients with CHF.

Key words: myoglobin, N-terminal Pro-B-Type natriuretic peptide, biomarkers; subclinical cardiomyocyte damage; hemodynamic stress; risk stratification.

INTRODUCTION

Modern cardiology continues to actively search for highly sensitive and pathogenetically grounded biomarkers for early diagnosis, risk stratification, and prediction of the course of heart failure (HF), which remains one of the leading causes of disability and mortality in the world. HF is a complex clinical syndrome that reflects not only hemodynamic dysfunction but also subclinical cardiomyocytes damage, which subsequently leads to progressive structural remodelling of the myocardium.

In current clinical guidelines, natriuretic peptides, in particular BNP and its N-terminal fragment NT-proBNP, are considered the gold standard of HF biomarkers, as they reflect the degree of hemodynamic overload and ventricular dysfunction. Measurement of NT-proBNP levels markedly improves diagnostic accuracy of HF diagnosis, has important prognostic value, and is used to monitor therapy effectiveness. However, these markers mostly reflect the functional state of the heart and do not provide sufficient information about early structural changes in

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cardiomyocytes. [1, 2].

In this context, interest is growing in biomarkers that directly reflect cellular myocardial damage. Myoglobin, a low-molecular-weight haemoprotein localized in cardiac and skeletal muscles, is rapidly released into the blood upon muscle cell damage, making it highly sensitive as a marker of early cytolysis. Although traditionally regarded as an early but nonspecific marker of acute myocardial infarction, recent studies have shown its potential role in reflecting chronic subclinical myocardial damage, particularly under conditions of prolonged hemodynamic and metabolic stress.

Accumulating data indicate that increased blood myoglobin levels can be observed not only in acute ischemic events but also in chronic cardiovascular conditions, often accompanied by a parallel rise in NT-proBNP, suggesting a combination of structural myocardial damage and functional overload [3]. Thus, combined assessment of these two biomarkers may be considered components of a single pathogenetic pathway: from subclinical cardiomyocyte cytolysis to the development of clinically significant heart failure [4].

Moreover, the modern concept of "precision cardiology" emphasizes the need for a multibiomarker approach that combines indicators of diverse pathophysiological processes - neurohumoral activation, inflammation, oxidative stress, and cellular damage [5]. In this context, integrating myoglobin as a marker of cytolysis with NT-proBNP as a marker of hemodynamic stress may substantially improve the sensitivity of early diagnosis and the accuracy of prognostication the course of HF.

Therefore, studying the relationship between myoglobin and NT-proBNP levels in patients with chronic heart failure is a relevant area of contemporary research, offering prospects for developing integrated diagnostic models and a personalized approach to patient management.

The aim of the study was to assess the relationship between plasma myoglobin and NT-proBNP in patients with chronic heart failure (CHF) of various etiologies to substantiate the concept of a single pathogenetic continuum of structural damage and hemodynamic stress of the myocardium.

METHODS

The study was conducted as a prospective, single-center, cross-sectional observational study with comparative analysis of biomarkers in patients with CHF of various genesis. All patients whose data were used in the study provided informed consent. The study was approved by the Commission on Bioethical Expertise and Ethics of Scientific Research of the O.O. Bogomolets National Medical University (Protocol No. 195 dated 05/26/2025).

The study involved 138 participants, including 123 patients with various clinical forms of CHF. The study design scheme is shown in Fig. 1. Of these, 93 patients had heart defects and were shown to perform cardiac surgery for valve pathology. For comparison, patients without pronounced valvular regurgitation were studied, their CHF was mainly related to ischemic myocardial damage, arterial hypertension, cardiomyopathies and impaired systolic and/or diastolic myocardial function, left ventricular remodelling, etc. Patients who developed postoperative thromboembolic complications were analysed as a separate subgroup. All patients

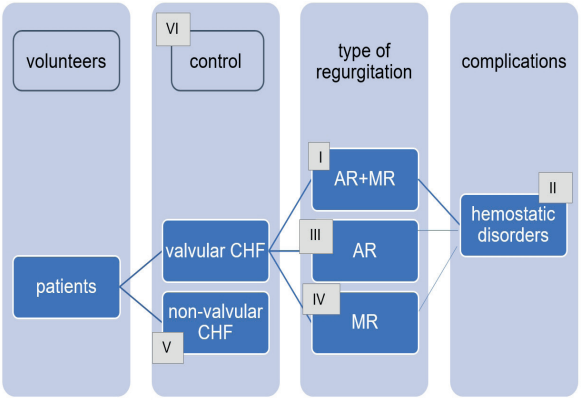


Fig. 1. Schematic of the main study group design. Notes: MR mitral regurgitation, AR - aortic regurgitation, CHF - chronic heart failure

received standard drug therapy in accordance with current clinical recommendations. Patients were divided into 6 main groups: Group I (n = 13) with combined valve pathology: mitral (MR) and aortic (AR) regurgitation. Group II are the patients who developed haemostasis-related complications during the 3rd day of observation after cardiac surgery (n = 15). In this group, the distribution of valve defects was as follows: MR - 4, AR - 7, AR + MR - 4. Group III - with AR (n = 36), Group IV - with MR (n = 29), Group V - patients with CHF of non-valvular genesis (n = 30). The control group VI consisted of relatively healthy volunteers of appropriate age and gender - 15 people.

Myoglobin levels (ng/ml) were measured by solid-phase enzyme-linked immunosorbent assay using a kit (3225-300, Myoglobin Test System, Monobind Inc., USA, Range 0.1-200 ng/ml, Sensitivity 0.178 ng/ml). NT-proBNP levels (pg/ml) were measured using a kit («ELISA Kit FineTest», China, EH0350, Range 39.063-2500 pg/ml, Sensitivity 23.438 pg/ml). Measurements were performed on a HiPo MPP-96 microplate photometer, ("Biosan", Latvia) with a 3D-IW8 Inteliwasher plate washer, ("Biosan", Latvia) and a PST-60HL-4 thermoshaker, ("Biosan", Latvia). Most variables showed nonparametric distributions, so statistical analysis was performed using nonparametric methods: multiple comparisons were conducted using the Kruskal–Wallis one-way ANOVA on ranks with Dunn's post hoc test. Data are presented as median and interquartile range Me [Q1; Q3]. Results are also presented as box-plot diagrams. Correlation analysis was performed using Spearman's test (R).

RESULTS AND DISCUSSION

In line with the study aim, we designed the investigation to compare known biomarkers of myocardial damage across six main patient groups, in which CHF development was determined by different etiological and pathophysiological mechanisms. According to the data presented in Table 1, patients were similar in age range and sex distribution, which was characterized on average by 65 [54-68.5] years with a predominance of males. A control group of volunteers without CHF was selected to match these characteristics.

Note: The statistical significance of differences was assessed using the Kruskal-Wallis test, the parameter "sex" was compared in the "k*m" contingency table using the $\chi 2$ test.

At the first stage of the study, marker levels were compared between patients with valvular and non-valvular pathology (Table 2). It was revealed that myoglobin was 1.89-fold ($P < 0.01$) higher in non-valvular CHF than in patients with valvular disease, in both groups, the myoglobin was significantly elevated versus the control: 1.4-fold ($P < 0.05$) in the valvular and 2.6-fold ($P < 0.01$) in the non-valvular group. A similar pattern was observed for NT-proBNP. In patients with non-valvular CHF, the marker levels were 1.3-fold ($P < 0.01$) higher than in patients with valvular disease and were

Table 1. Characteristics of the groups by age and sex of study participants Me [QI÷QIII]

Data of participants	Control	Combined valve pathology	Thromboembolic complications	Aortic regurgitation	Mitral regurgitation	Chronic heart failure
Number of participants, % male participants	n = 15 (65%)*	n = 13 (67%)*	n = 15 (87%)*	n = 36 (56%)*	n = 29 (70%)*	n = 30 (60%)*
Age Me; [QI÷QIII] (Min - Max)	67 [55-72] (46-78) **	68 [62-69] (47-74) **	59 [53-67] (49-68) **	66 [56-70] (32-78) **	59 [45-68] (23-74) **	70.5 [60.5-74] (44-86) **

Age did not differ significantly among the groups (Kruskal–Wallis test, $p > 0.05$). Sex distribution also did not differ among the groups (Pearson's χ^2 test, $p = 0.974$).

Table 2. Marker levels in comparison groups by CHF etiology

Marker	Control 1	Valvular pathology 2	Non-valvular pathology 3	Significance of differences
Myoglobin, ng/ml	34.00 [25.78 43.08]	47.1 [39.8-61.0]	87.97 [68.46-124]	P_1-P_3 <0,01 P_1-P_2<0,05 P_2-P_3<0,01
NT-proBNP, pg/ml	82.8 [68.1-117.6]	650 [371-895]	863[653-1856]	P_1-P_2 <0,01 P_1-P_3<0,01 P_2-P_3<0,01

in 10-fold ($P < 0.01$) and in 7.8-fold ($P < 0.01$) higher than controls in the non-valvular and valvular groups, respectively.

We then analysed a separate group of patients with heart defects who underwent cardiac surgery and developed postoperative complications such as retinal artery occlusions, indicative of haemostatic disturbance (Table 3). It was revealed that both markers were elevated in the groups with complications but not significantly compared to those whose surgery was uncomplicated. The difference in myoglobin levels was 20%, and NT-proBNP levels was 30%.

Thus, we found that levels of markers considered the "gold standard" for diagnosing cardiomyocyte damage and hemodynamic disorders differ significantly among CHF patients whose disease has different etiological factors and predominant pathophysiological mechanisms. We then analysed and compared marker levels in patients with valvular disease in the context of different types of regurgitation, but these data are presented on a blot diagram of all 6 groups data (Fig. 2).

In patients with combined valvular pathology (Fig. 2A), myoglobin levels were 60.31 [53-67.45] ng/ml, which is 1.8-fold ($P < 0.01$) higher than in controls. A similar value was observed in the group with postoperative arterial occlusions - 56.88 [47.9-67] ng/ml. In patients with AR, the myoglobin levels were 43.72 [38.6-69.7] ng/ml, and in those with MR it was 39.81 [37.09-47.1] ng/ml, which was the lowest in the patient group and did not differ significantly from controls, but was 2.2-fold ($P < 0.01$) lower than in the non-valvular CHF group.

NT-proBNP levels (Fig. 2B) were maximal 1034.00 [719-1123] pg/ml in the combined valve pathology group. In patients with MR the levels were 792.00 [407-946] pg/ml, whereas in the AR group it was 2-fold lower - 396.00 [321-562.5] pg/ml. Despite the high marker dispersion, the

Table 3. Marker levels in comparison groups by presence of hemostasis disorders and postoperative complications

Marker	Control 1	Valvular pathology without complication 2	Valvular pathology with complications 3	Non-valvular pathology 4	Significance of differences
Myoglobin, ng/ml	34.00 [25.78-43.08]	45.81 [38.54-65]	56.88 [47.9-67]	87.97 [68.46-124]	P_1-P_3<0,01 P_2-P_4<0,01 P_3-P_4<0,01
NT-proBNP, pg/ml	82.8 [68.1-117.6]	551 [354-903]	785 [563-885]	863 [653-1856]	P_1-P_3<0,01 P_1-P_4<0,01 P_2-P_4<0,01 P_3-P_4<0,01

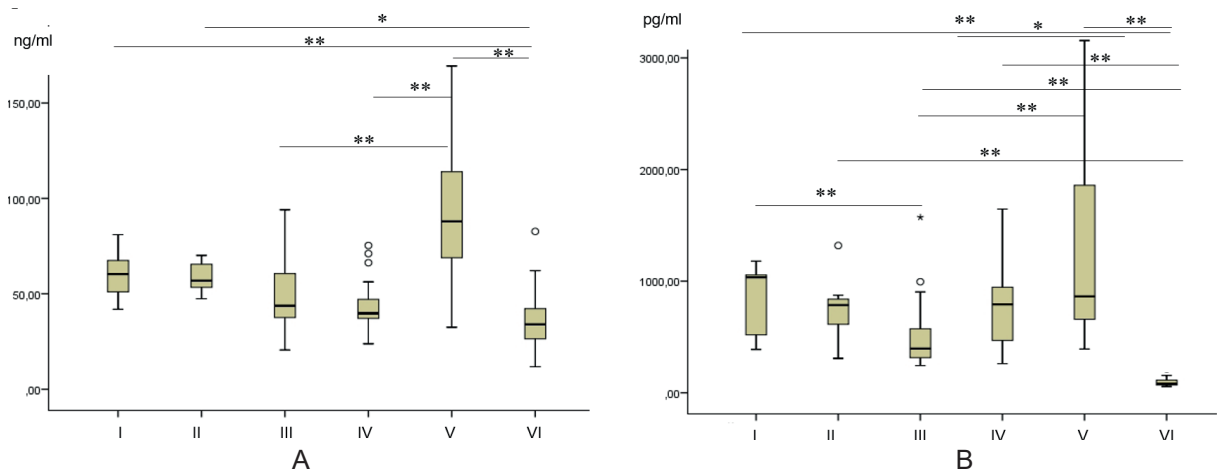


Fig. 2. Myoglobin (A) and NT-proBNP (B) levels in blood plasma of the study participants. Note: *P < 0.05, **P < 0.01

values differed significantly between groups.

A significant positive correlation was found between myoglobin and NT-proBNP R = 0.397 (P < 0.001).

To assess the association between myoglobin and signs of severe heart failure, ROC analysis was performed using a NT-proBNP threshold of >900 pg/ml as the upper reference limit for study participants of the indicated age.

ROC analysis (Fig. 3) demonstrated a statistically significant association between myoglobin levels and the presence of signs of heart failure, defined by NT-proBNP >900 pg/ml. The area under the ROC curve was 0.687 (95% CI 0.581–0.792; P = 0.001), indicating marker's moderate discriminatory ability. These results suggest the role of myoglobin as a potential biomarker associated with myocardial injury in patients with heart failure.

The data indicate a moderate association between elevated myoglobin and worsening signs of heart failure and myocardial damage, as reflected by NT-proBNP more than 900 pg/ml.

In patients with CHF, a significant increase in myoglobin and NT-proBNP levels was found compared to the control (P < 0.05), reflecting combined mechanisms of structural myocardial damage and neurohumoral activation of peptides. However, a certain difference in markers was revealed in groups with different etiological factors of CHF.

Although myoglobin is traditionally regarded as a sensitive marker of early muscle injury, it is not cardiac-specific and may increase in various conditions including skeletal muscle damage, renal dysfunction, systemic inflammation, tissue hypoxia, perioperative stress, and thromboembolic complications. Therefore, interpretation of elevated myoglobin levels in CHF should consider the potential contribution of extracardiac mechanisms.

Comparison of biomarker content in groups with isolated MR and AR confirms the idea of

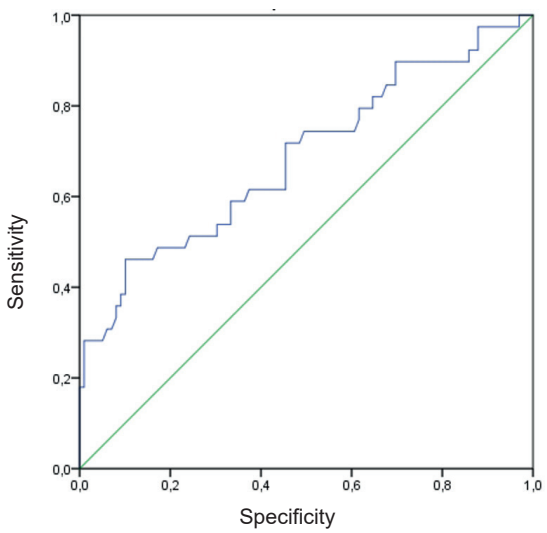


Fig. 3. ROC curve demonstrating a statistically significant association between myoglobin levels and the presence of signs of heart failure, defined by NT-proBNP concentration >900 pg/ml

pathogenetic informativeness of markers [6, 7]. Higher NT-proBNP levels in patients with mitral regurgitation reflect a state of volume overload and increased cardiac filling pressure, accompanied by myocardial distension and activation of natriuretic peptides. The peptide level is known to correlate with chamber dilation, filling pressure, left ventricular mass, severity of mitral regurgitation, etc [6].

In contrast, aortic regurgitation is dominated by prolonged chronic left ventricular overload with increased systolic wall tension and impaired coronary perfusion. The mechanisms of eccentric left ventricular hypertrophy, increased wall tension in systole, which creates conditions for a local decrease in coronary perfusion, the emergence of zones of subendocardial ischemia, are described [7]. Thus, the dissociation between myoglobin and NT-proBNP levels reflects distinct pathophysiological components - structural damage and hemodynamic overload of the myocardium.

In patients with combined heart defects, both mechanisms described above lead to a significant increase in both biomarkers, which emphasizes the integration of the pathophysiological components of cardiac damage. These patients were analyzed as an exploratory subgroup to assess the potential association between biomarker levels and haemostatic disturbances following cardiac surgery. An interesting finding was the significant increase in myoglobin and NT-proBNP in patients who developed arterial occlusions following cardiac surgery for heart valve replacement. The study [8] describes the features of the plasminogen/plasmin system in this cohort of patients and shows that postoperative thrombus formation and high functional activity of plasmin are combined with the individual property of connective tissue to express MMP-9 against the background of insufficient activity of the metalloprotease inhibitor TIMP-3. This haemostatic state may contribute to vascular matrix degradation, impair thrombus stabilization, and promote thrombus detachment with subsequent occlusion of smaller vessels [8].

In addition, postoperative thromboembolic complications may further contribute to elevated myoglobin concentrations through ischemic tissue injury and microvascular hypoperfusion. Therefore, increased myoglobin levels observed in this subgroup should be interpreted cautiously and may reflect a combination of cardiac and extracardiac mechanisms associated with the postoperative state.

Thus, the described features of hemostasis are consistent with the increased NT-proBNP and myoglobin levels, which reflect distinct but interrelated links in pathogenesis. An increase in NT-proBNP characterizes hemodynamic overload and congestion associated with activation of plasminogen activator inhibitor-1 and suppression of fibrinolysis [9]. At the same time, elevated myoglobin, as a biomarker potentially associated with myocardial and systemic tissue injury, may reflect activation of proteolytic processes, particularly MMP-9, which promote extracellular matrix degradation [10]. The combination of suppressed fibrinolysis with increased proteolytic activity creates conditions for the formation of a structurally unstable thrombus, which is not amenable to effective lysis, but has an increased tendency to fragmentation and embolization in the retinal artery.

The highest myoglobin values detected in non-valvular CHF (2.6-fold higher than controls) indicate a pronounced persistent structural-metabolic stress and a possible phenomenon of chronic microcytolysis of cardiomyocytes in this disease etiology. High NT-proBNP concentration in patients with non-valvular CHF reflects a high degree of hemodynamic overload of the heart. A statistically significant positive correlation between myoglobin and NT-proBNP levels ($R = 0.397$; $P < 0.001$) confirms their interrelation as markers of different but integrated links in the pathogenesis of CHF. Thus, the obtained results suggest the presence of interrelated pathophysiological processes in which mechanical myocardial overload may

contribute to myocardial structural stress and persistent subclinical structural-metabolic alterations.

These findings reveal new facets of understanding of pathogenetic cascade of heart failure, where myoglobin acts not merely as an inert marker of damage but as an active indicator of structural-metabolic destabilization of the myocardium. This also speaks in favour of changing the traditional view of myoglobinemia as a transient phenomenon, which is characteristic only for acute myocardial infarction.

Probably, long before the appearance of macroscopic areas of necrosis, cardiomyocytes are subjected to persistent structural stress that permits leakage of low-molecular-weight proteins through destabilized sarcolemma. This process directly depends on the degree of stretching of the heart chambers, as evidenced by the correlation with NT-proBNP.

The current stage of laboratory medicine is marked by a shift from single biomarkers to integrated multicomponent panels that reflect different pathogenetic links of the disease. This is especially relevant with the rise of omics technologies, which enable the development of biomarker signatures for patient stratification [11]. In contemporary cardiology, there is likewise a tendency to move from isolated biomarkers use to combined panels to reflect different pathogenetic links of the disease [12, 13]. In this context, the combination of NT-proBNP and myoglobin can be viewed as a parsimonious yet pathogenetically justified biomarker model. NT-proBNP reflects the degree of hemodynamic overload and myocardial strain, while myoglobin is an indicator of subclinical cardiomyocyte damage. Their simultaneous determination permits an integral assessment of the functional and structural components of cardiac pathology. The identified dissociation between the levels of these markers in patients with different profiles indicates the existence of different pathophysiological phenotypes of chronic heart failure and can be used for risk stratification, regarding the development of thromboembolic complications.

The obtained results support the concept of potentially interconnected pathophysiological mechanisms in which mechanical myocardial overload is associated with structural myocardial damage and the development of structural-metabolic destabilization. Myoglobin may be considered as a potential biomarker of chronic subclinical myocardial damage in CHF, complementing information obtained from NT-proBNP determination and expanding possibilities of pathogenetically oriented stratification of patients.

Limitations of the study include the single-center design, the lack of prospective assessment of clinical endpoints, and the small size of some subgroups. The latter limits the ability to perform a proper multivariate regression analysis while simultaneously accounting for all potential factors influencing the outcome. Including a large number of predictors with a limited sample size may lead to overfitting of the model and instability of the regression coefficients.

Therefore, further research in this direction requires validation of the results in larger cohort studies.

CONCLUSIONS

1. Significantly increased myoglobin and NT-proBNP levels were observed in patients with CHF compared with controls, reflecting a combination of processes of subclinical cardiomyocyte damage and hemodynamic myocardial overload.

2. A statistically significant positive correlation between the markers was revealed ($R = 0.397$), along with a statistically significant association between myoglobin level and NT-proBNP >900 pg/ml. The area under the ROC curve was 0.687 (95% CI 0.581–0.792), supporting the interrelatedness of these markers as distinct but complementary components of interrelated pathophysiological processes in CHF development.

3. The established dissociation of myoglobin and NT-proBNP levels in patients with different genesis of HF indicates the presence of distinct pathophysiological phenotypes of the disease, reflecting the dominance of either hemodynamic overload or structural myocardial damage.

4. Combined measurement of myoglobin and NT-proBNP can be considered as a parsimonious, pathogenetically justified biomarker model that enables integrated assessment of myocardial functional and structural status, has potential for risk stratification, in particular, regarding the development of thromboembolic complications in patients with CHF, and may serve as a basis for further research into personalized biomarker stratification.

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ПАТОФІЗІОЛОГІЧНА ОЦІНКА СТРУКТУРНОГО ПОШКОДЖЕННЯ МІОКАРДА ТА ГЕМОДИНАМІЧНОГО ПЕРЕВАНТАЖЕННЯ

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Сучасна кардіологія активно шукає ефективні підходи до ранньої діагностики та прогнозування серцевої недостатності, яка залишається провідною причиною інвалідизації та смертності, і разом із усталеними маркерами гемодинамічного стресу натрій-уретичним пептидом (BNP/NT-proBNP) зростає інтерес до міоглобіну як потенційного індикатора структурного ушкодження міокарда. Мета нашої роботи оцінити взаємозв'язок вмісту міоглобіну в плазмі та NT-proBNP у пацієнтів із хронічною серцевою недостатністю різної етіології та обґрунтувати концепцію інтегрованого патофізіологічного континууму пошкодження міокарда та гемодинамічного стресу. Проспективне одноцентрове обсерваційне дослідження поперечного типу включало 138 учасників, з яких 123 пацієнти мали хронічну серцеву недостатність (ХСН) різного походження, а 15 практично здорових людей, які ввійшли у контрольну групу. Пацієнти були стратифіковані на групи відповідно до етіології ХСН (клапанна та неклапанна) та з тромбоемболічними ускладненнями. Вміст міоглобіну та NT-proBNP у плазмі вимірювали за допомогою імуноферментного аналізу. Статистичний аналіз включав непараметричні тести та кореляційний аналіз. У пацієнтів із ХСН спостерігалися значно вищі концентрації міоглобіну та NT-proBNP порівняно з контрольною групою. Вміст міоглобіну був найвищим у пацієнтів з неклапанною ХСН (збільшення у 2,6 раза порівняно з контролем), що свідчить про стійке структурне та метаболічне напруження міокарда. Вміст NT-proBNP був значно підвищеним у всіх групах з ХСН, але найвищі значення спостерігали у пацієнтів з комбінованою клапанною патологією. Виявлена значна позитивна кореляція між вмістом міоглобіну та NT-proBNP (r = 0,397). ROC-аналіз продемонстрував статистично значущий зв'язок між вмістом міоглобіну та наявністю ознак серцевої недостатності, що визначалися як NT-proBNP >900 пг/мл, 0,687 (95% ДІ 0,581–0,792), що вказує на помірну дискримінаційну здатність маркера. Комбінована оцінка вмісту міоглобіну та NT-proBNP відображає взаємодоповнюючі аспекти патофізіології ХСН, інтегруючи структурне пошкодження міокарда та гемодинамічний стрес. Цей підхід з двома маркерами являє собою мінімальну, але патогенетично обґрунтовану модель, яка може покращити стратифікацію ризику та сприяти розробці персоналізованих діагностичних стратегій при ХСН.

Ключові слова: міоглобін; N-кінцевий натрійуретичний пептид Pro-B-типу, біомаркери; субклінічне ушкодження кардіоміоцитів; гемодинамічний стрес; стратифікація ризику.

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