Endothelial microvascular dysfunction and its relationship with the level of haptoglobin in patients with different phenotypes of chronic heart failure

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Aim. To study the relationship between the level of haptoglobin and the main indicators of microcirculation (MC) in patients with different phenotypes of chronic heart failure (CHF).
Materials and methods. Patients with different phenotypes of functional class II-IV chronic heart failure according to NYHA (n=80) underwent a general clinical examination, determination of the serum haptoglobin level by enzyme-linked immunosorbent assay, as well as an assessment of the MC state on the medial surface of the upper third of the leg by laser Doppler flowmetry (LDF).
Results. Patients with CHF included patients with preserved left ventricular ejection fraction (HFpEF; n=27, intermediate ejection fraction (HFmrEF; n=25) and reduced ejection fraction (HFrEF; n=28). The median value of haptoglobin in the HFpEF group was 1387.6 [747.5; 1946.9] mg/l, in the HFmrEF group was 1583.4 [818.9; 2201.4] mg/l, in the HFrEF group was 968.5 [509.5; 1324.4] mg/l. Correlation analysis revealed statistically significant relationships between haptoglobin and the amplitudes of the endothelial frequency range (Ae) in the groups of HFmrEF (r=-0.628, 95% confidence interval [CI] -0.256; -0.825, p=0.003) and HFrEF (r=-0.503, 95% CI -0.089; -0.803, p=0.02). A negative relationship between the haptoglobin level and Kv and σ was revealed, as well as a formula for calculating the value of haptoglobin was obtained, which is predicted on the basis of the amplitude index of the endothelial frequency range: [haptoglobin]=1787-(4053×Ae).
Conclusion. The multifactorial effect of haptoglobin is realized in the central and peripheral mechanisms of MC regulation. Low values of haptoglobin in blood plasma should be considered as a potential marker for the development of complications and used in a comprehensive assessment of the state of patients with CHF. Evaluation of the diagnostic and prognostic significance of haptoglobin, especially in patients with HFmrEF, requires further study.

Key words: chronic heart failure, ejection fraction, microcirculation, haptoglobin, endothelial dysfunction.

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Introduction

In recent years, the relationship between inflammation and the onset, course and prognosis of chronic heart failure (CHF) has attracted increasing attention of researchers [1,2]. One of the pro-inflammatory acute-phase blood plasma proteins synthesized by the liver is haptoglobin, first described by M. Polonovski and M.F. Gayle in 1938 [3]. Later, haptoglobin was found in immune cells (neutrophils and monocytes), as well as in adipocytes [4-7].

The main haptoglobin function, which belongs to the alpha-2-globulin fraction, is to reduce the toxicity of free forms of hemoglobin and myoglobin, which are powerful oxidants. The toxicity of free hemoglobin, which is in plasma outside of erythrocytes, is manifested by an overload of the body with products of its destruction, namely, iron, bilirubin, porphyrins, activation of free radical oxidation processes, disruption of ATP synthesis and tissue hypoxia. The ability to form a complex [hemoglobin-haptoglobin], which is recognized by the scavenger-receptor of macrophages CD163, ensures the capture of hemoglobin by the reticuloendothelial system of the spleen and macrophages and its splitting into globin and heme, the further destruction of which is carried out in the liver with the participation of hem-oxygenase and biliverdin reductase [6-10]. The amount of haptoglobin circulating in the blood plasma of a healthy person is sufficient to bind up to 3 g of free hemoglobin [11], and its content increases significantly under conditions of inflammation. Violation of this mechanism leads to the fact that freely circulating hemoglobin, heme and iron begin to participate in redox reactions, which in turn leads to the release of free radicals with powerful oxidative activity. This contributes to the development of immune-inflammatory syndrome, damage to the capillary endothelium and circulatory hypoxia, which is interrelated with microcirculatory disorders in CHF [11-13]. But so far there are no studies for assessing the haptoglobin level in patients with CHF and its correlation with microcirculatory dysfunction, which determined the aim of our study: investigation the relationship between the haptoglobin level and the main indicators of microcirculation (MC) in patients with different phenotypes of CHF.

Materials and methods

The study included 80 patients with CHF admitted to the cardiology and internal medicine department of the University Clinical Hospital No. 4 (Sechenov University).

Inclusion criteria: CHF of II-IV functional class (NYHA), complicating the course of coronary heart disease (CHD) and/or arterial hypertension (AH), lasting at least 6 months, patients were over 18 years old.

Exclusion criteria: malignant neoplasms, including lymph and myeloproliferative; severe renal failure requiring hemodialysis; type 1 diabetes mellitus; moderate to severe anemia; skin lesions in the area of application of the light probe.

The functional class (FC) of CHF was assessed according to the clinical condition assessment scale modified by V.Yu. Mareev [1]. The patients underwent a standard general clinical examination, which included general and biochemical blood tests, general urine analysis, coagulogram, electrocardiographic examination, ultrasound examination of the abdominal cavity and kidneys, chest x-ray, and in the first 1-2 days of hospitalization, all patients were determined by the level of N- terminal fragment of brain natriuretic peptide (B-type; NT-proBNP) in blood plasma by enzyme-linked immunosorbent assay (BNP-fragment, Biomedica, Austria), as well as the level of haptoglobin by enzyme-linked immunosorbent assay (Assay Max Human Haptoglobulin ELISA, USA). Echocardiographic examination was carried out on a TOSHIBA XARIO SSA-660A apparatus (Japan) according to the standard technique recommended by the American and European Society of Echocardiography [14]. Left ventricular ejection fraction (LVEF) was determined by the Simpson method. According to the value of LVEF, the patients were divided into 3 groups corresponding to CHF phenotypes: with preserved LVEF⩾50% (HFpEF), mid-range LVEF is 40-49% (HFmrEF) and reduced LVEF<40% (HFrEF) [1].

The state of the MC was studied on the medial surface of the upper third of the leg in the sitting position of the patient by the LDF method using a laser analyzer «LAZMA-PF» (NPP Lazma, Moscow), which ensures the determination of microcirculation indicators in relative (perfusion) units (this indicator is 7-20 relative units at a blood flow velocity of 0.8-4.5 mm/s with a tolerance limit of ±20%) at a continuous laser radiation power at the analyzer output of no more than 1 mW and a wavelength of 850 nm. The study was carried out under standardized conditions: in a room with a temperature of +24±1ºC, for 15 minutes, after a 20 minutes adaptation period; all study participants refrained from eating food, caffeinated and alcoholic beverages, smoking and exercising at least 2 hours before the study.

After measuring the main parameters of the MC by the LDF method, such as the constant component of perfusion, the nutritive component of microcirculation and the shunt component of the microcirculation, the segments of the LDF-gram recording were analyzed for artifacts, a filter based on the gyroscope and respiratory sample data was applied, and using the LDF 3.1 software LAZMAMC (NPP Lazma, Moscow) root-mean-square deviations of perfusion fluctuations (σ) and coefficients of variation (Kv) were calculated automatically, and the wavelet transform method was carried out, which is digital signal processing with the construction of a surface in three-dimensional space (frequency-time-coefficient) or a graph in two-dimensional (frequency-coefficient) space (Fig. 1) to highlight the frequencies of active and passive factors of regulation, determine the power of their spectra and assess the contribution of each of them to the resulting power of the total signal [15,16].

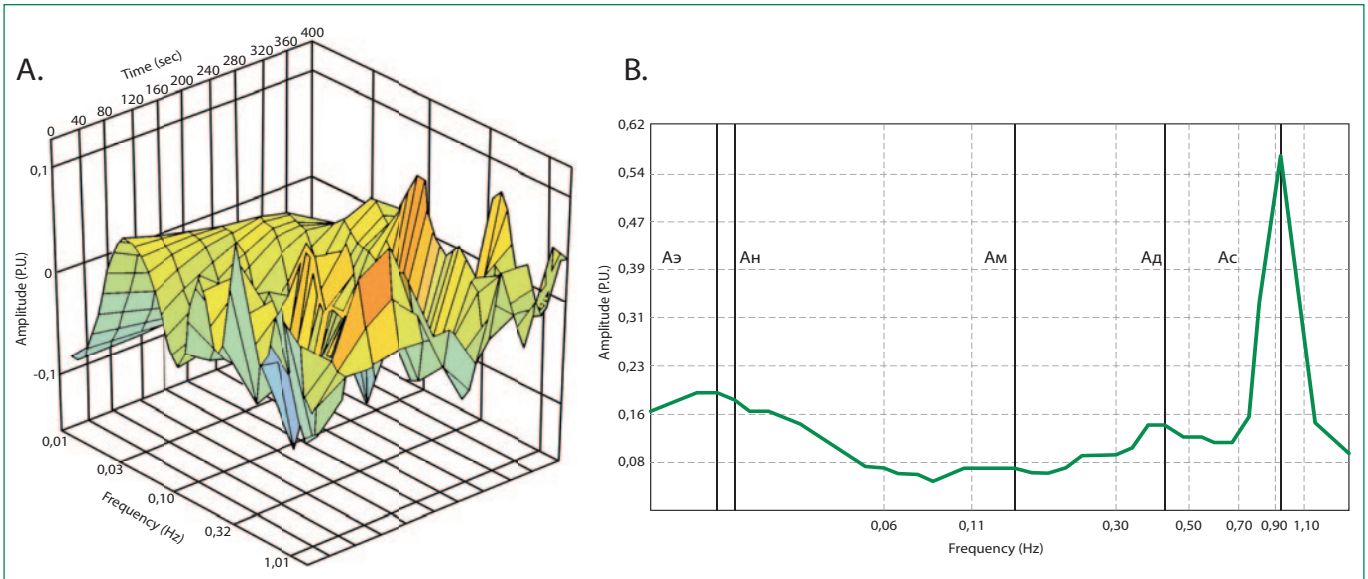
According to the results of the wavelet transform, in the frequency range of registration 0.007-1.6 Hz, the ranges were ranked corresponding to active regulation factors – endothelial (0.007-0.017 Hz), sympathetic (0.023-0.046 Hz), myogenic (0.06-0.15 Hz), constituting, as well as passive and forming outside the microcirculation system, respiratory (0.21-0.6 Hz) and cardiac (0.7-1.6 Hz), constituting the frequency spectrum of regulatory activity [15,16]

During LDF, the installation of the light guide probe can be performed on an arbitrary area of the skin surface, depending on the objectives of the study, therefore the method has no restrictions on the choice of the tested area [15]. 15 (18.8%) patients in our study had increased risks of developing obliterating atherosclerosis of the vessels of the lower extremities due to the combination of hypertension, coronary artery disease, and type 2 diabetes mellitus. Also, some of the patients who took part in the study had signs of severe CHF, manifested not only by peripheral edema, but also by lymphorrhea. We chose the medial surface of the upper third of the leg, rather than the «standard point» on the dorsum of 1 toe, as the point of registration of the MC parameters.

There were no data on the normal values characteristic of the LDF-gram registration point that we chose, so 15 healthy volunteers aged 48±9 years old, without bad habits and without symptoms of cardiovascular, oncological, respiratory, autoimmune diseases, anemia and renal failure, was included in the study as a control group.

The study was approved by the local ethics committee at the Moscow State Medical University named after I.M. Sechenov, Ministry of Health of the Russian Federation (Sechenov University) (protocol No. 31-20). The study was carried out in accordance with the standards set by the Declaration of Helsinki and Good Clinical Practice. All participants gave written informed consent.

Statistical analysis of the data obtained was carried out using the Statistica 12 software (StatSoft Inc., USA). The data were analyzed for normality of distribution by the method of estimating the coefficients of skewness



The amplitude-frequency spectra obtained using 3D (A) and 2D (B) wavelet transform of the initial 15-minute LDF signal of the cutaneous blood flow signal (fragment of the coefficients from the 10th to the 15th minute) are presented, illustrating the presence of separate spectral peaks, the frequencies and amplitudes of which change over time.

Figure 1. Graphical representation of 3D (A) and 2D (B) wavelet transform of laser Doppler flowmetry image

and kurtosis, as well as by graphical methods. The Kruskal-Wallis test (one-way ANOVA) with subsequent analysis of pairwise differences was applied to identify statistically significant differences between groups. Pearson's method for normal distribution and Spearman's method for abnormal distribution were used to identify correlations. A bootstrap analysis with a 95% confidence interval (CI) with bias correction and acceleration was applied to obtain the most accurate correlation estimates and extend the results to the entire population. One-way regression analysis was used to construct a haptoglobin regulation model. Differences were considered statistically significant at $p<0.05$.

Results

Clinical and demographic characteristics of patients with CHF are presented in Table. 1.

Most of the patients were overweight or obese 1-2 degrees, some had type 2 diabetes mellitus. Cardiac arrhythmias (paroxysmal or persistent atrial fibrillation or high-grade ventricular extrasystoles) were found in more than half of the patients.

Isolation of CHF phenotypes by the degree of left ventricular systolic dysfunction revealed HFpEF in 27 (33.75%) patients, HFmrEF in 25 (31.25%) patients, HFrEF in 28 (35.0%) patients. Patients in the identified phenotypic groups were comparable in terms of gender, age, and basic biochemical parameters (Table 2).

According to the results of enzyme immunoassay, statistically significantly lower levels of haptoglobin were noted in the HFrEF group.

Table 1. Clinical and demographic characteristics of patients with CHF (n=80)

Parameter	Value
Age, years	72±11
Men, n (%)	39 (54)
BMI, kg/m^2	32.0 [25.0; 47.2]
Type 2 diabetes mellitus, n (%)	15 (18.8)
Heart rhythm disturbances[a], n (%)	46 (57.6)
LVEF, %	44 [38; 55]
Functional class of chronic heart failure (NYHA), n (%)	
II	56 (70)
III	16 (20)
IV	8 (10)

Data are presented as M±SD or Me [25%; 75%], unless otherwise stated

BMI – body mass index, LVEF – left ventricular ejection fraction, NYHA – New York Heart Association, CHF – chronic heart failure.

[a] paroxysmal or persistent atrial fibrillation, high-grade ventricular extrasystoles

Comparative analysis of changes in the levels of biologically active molecules involved in the pathogenesis of CHF showed us a clear tendency to increase the concentration of NT-proBNP as the signs of systolic dysfunction of the LV myocardium in CHF patients worsened. No similar trends in the haptoglobin level were observed: the maximum concentrations of the haptoglobin level were detected with HFmrEF, and the minimum concentrations were found with HFrEF. At the same time, there was no dependence of the level of haptoglobin on the value of the glomerular filtration rate.

Comparative analysis of the state of the MC showed the absence of statistically significant differences in the

Table 2. Comparative clinical and laboratory characteristics of patients with different CHF phenotypes

Parameter	HFpEF (n=27)	HFmrEF (n=25)	HFrEF (n=28)
Age, years	76 [65; 83]	74 [61; 80]	72 [67; 82]
Men/Women, n (%)	9 (33.3)/18 (66.7)	10 (40)/15 (60)	18 (64.3)/10 (35.7)
BMI, kg/m2	29.2 [25.6; 34.6]	36 [26.5; 47.2]	26 [22.4; 36.0]
Glucose, mmol/l	5.7 [5.0; 6.5]	6.6 [5.7; 7.5]	6.3 [5.2; 7.7]
Total cholesterol, mmol/l	5.47 [3.97; 6.12]	4.97 [3.35; 6.19]	4.19 [3.26; 5.76]
Hemoglobin, g/l	134 [129; 143]	133 [115; 140]	136 [121; 140]
GFR, ml/min/1.73m2	55.3 [43.0; 61.5]	47.1 [32.1; 57.1]	48.5 [39.0; 57.0]
NT-proBNP, pg/ml	786 [439; 1480]	1939 [1101; 3021]*	2112 [1463; 4525]*†
Haptoglobin, mcg/ml	1387.6 [747.5; 1946.9]	1583.4 [818.9; 2201.4]	968.5 [509.5; 1324.4] *†

Data are presented as Me [25%; 75%], unless otherwise stated

* — $p<0.05$ when compared with the HFpEF group

† — $p<0.05$ when compared with the HFmrEF group

HFpEF – heart failure with preserved ejection fraction, HFmrEF – heart failure with mid-range ejection fraction, HFrEF – heart failure with reduced ejection fraction, BMI – body mass index, GFR – glomerular filtration rate (CKD-EPI), NT-proBNP – N-terminal precursor of natriuretic peptide, CHF – chronic heart failure

microcirculation index in CHF patients with varying degrees of LV systolic dysfunction and in healthy people (Table 3). But we noted a significant decrease in Kv in patients with CHF. Evaluation of differences in MC indices showed statistically significant differences between the control group and patients with CHF with LVEF<50% for Kv, as well as for active factors of MC regulation (Ae, An, Am).

The results of the correlation analysis of haptoglobin parameters and microcirculation parameters in patients with different CHF phenotypes are presented in Table 4.

The data were bootstrapped to confirm correlations over a large sample size to calculate 95% CI for haptoglobin and MC correlations. In the group of HFpEF patients, no correlations between the level of haptoglobin and MC indicators were found. A significant moderate inverse relationship between the levels of haptoglobin and the amplitudes of the endothelial frequency range (Ae) was found in CHF patients with LVEF <50%: with HFmrEF - r=-0.628 [95% CI -0.256; -0.825]; p=0.003; with HFrEF - r=-0.503 [95% CI -0.089; -0.803], p=0.02.

One-way linear regression analysis was used to determine the strength and direction of the relationship, as well as to build a model for the regulation of the dependent variable [haptoglobin] from the independent variable [Ae], the results of which are presented in Table 5 and Fig. 2.

Thus, the predicted haptoglobin value will be calculated using the formula:

$[haptoglobin] = b_0+(b_{1x} Ae)$

Although the correlation of haptoglobin with the amplitude of the cardiac frequency spectrum (Ac) was statistically significant, it didn't show a statistically significant CI during bootstrapping, unlike other correlations we obtained.

Discussion

It's known that the development and progression of CHF occurs together with a violation of the processes of regulation of microcirculation both at the central and peripheral levels [1-2, 16], which leads to a change in tissue perfusion and activation of free radical reactions, including those with the participation of acute phase protein haptoglobin, which has important biological effects (binding hemoglobin, protecting cells from toxic radicals, inhibiting the action of nitric oxide, preventing kidney damage, stimulating and maintaining angiogenesis and immunomodulatory effects) [17,18]. It's assumed that haptoglobin may play a significant role in the progression of CHF, but the data regarding the dynamics of this biochemical indicator in patients with diseases of the cardiovascular system are very contradictory. For example, in a large Swedish population-based study as part of the Malmö Prevention Project, a follow-up of 6071 patients for over 22 years showed that an increase in the concentration of 5 acute-phase pro-inflammatory proteins (fibrinogen, ceruloplasmin, haptoglobin, orosomucoid and alpha1-antitrypsin) is

Table 3. Basic parameters of microcirculation in patients with different CHF phenotypes and in the control group

Parameter	HFpEF (n=27)	HFmrEF (n=25)	HFrEF (n=28)	Control group (n=15)
MI, P.U.	7.38 [6.53; 8.76]	8.00 [6.34; 8.64]	6.70 [6.00; 7.98]	6.32 [5.54; 7.94]
M_{nutr}	1.74 [1.27; 2.50]	2.18 [1.52; 2.45]	1.47 [1.36; 2.06]*‡	2.25 [1.55; 3.31]
M_{shunt}	5.54 [4.31; 6.84]*	5.21 [4.72; 6.03]*	5.05 [4.45; 6.02]*	3.99 [1.55; 3.31]
Kv, %	7.17 [5.58; 9.85]*	5.36 [4.52; 6.26]*†	7.51 [5.42; 9.76]*†‡	8.44 [7.23; 9.25]
σ, P.U.	0.48 [0.34; 0.77]	0.42 [0.30; 0.57]	0.48 [0.34; 0.72]	0.46 [0.41; 0.74]
Ae, P.U.	0.11 [0.06; 0.15]	0.07 [0.05; 0.08]*†	0.08 [0.06; 0.11]*	0.15 [0.11; 0.21]
An, P.U.	0.13 [0.10; 0.22]	0.11 [0.05; 0.15]*†	0.12 [0.08; 0.17]*	0.24 [0.13; 0.38]
Am, P.U.	0.18 [0.10; 0.21]	0.15 [0.09; 0.18]*	0.10 [0.09; 0.15]*†	0.20 [0.13; 0.31]
Ar, P.U.	0.15 [0.12; 0.19]	0.14 [0.12; 0.21]	0.15 [0.11; 0.19]	0.16 [0.11; 0.17]
Ac, P.U.	0.25 [0.22; 0.38]	0.21 [0.17; 0.29]	0.27 [0.19; 0.39]	0.19 [0.18; 0.26]

Data are presented as Me [25%; 75%]

* — p <0.05 when compared with the control group, † — p <0.05 when compared with the first group, ‡ — p <0.05 when compared with the second group

HFpEF – heart failure with preserved ejection fraction, HFmrEF – heart failure with mid-range ejection fraction, HFrEF – heart failure with reduced ejection fraction, MI – microcirculation index, M_{nutr} – microcirculation nutrient component, M_{shunt} – microcirculation shunt component, σ – standard deviation of perfusion fluctuations, Kv –variation coefficient, Ae – amplitude index of the endothelial frequency range, Am – amplitude index of the myogenic frequency range, An – amplitude index of the neurogenic frequency range, Ar – amplitude index of the respiratory frequency range, Ac – amplitude index of the cardiac (heart) frequency range

Table 4. Correlation coefficients of haptoglobin levels and microcirculation indices in patients with different CHF phenotypes

Parameter	HFpEF (n=27)	HFmrEF (n=25)	HFrEF (n=28)
	Haptoglobin level		
MI, P.U.	-0.384	-0.300	-0.176
M_{nutr}	-0.176	-0.258	0.181
M_{shunt}	-0.224	-0.241	-0.283
Kv, %	-0.293	-0.604*	-0.184
σ, P.U.	-0.317	-0.613*	-0.266
Ae, P.U.	-0.129	-0.628*	-0.503*
An, P.U.	-0.055	-0.315	-0.122
Am, P.U.	-0.015	-0.435	0.035
Ar, P.U.	0.150	-0.314	-0.022
Ac, P.U.	-0.109	-0.471*	-0.317

* - $p<0.05$ (Spearman's correlation coefficients)

HFpEF – heart failure with preserved ejection fraction, HFmrEF – heart failure with mid-range ejection fraction, HFrEF – heart failure with reduced ejection fraction, MI – microcirculation index, M_{nutr} – microcirculation nutrient component, M_{shunt} – microcirculation shunt component, σ – standard deviation of perfusion fluctuations, Kv –variation coefficient, Ae – amplitude index of the endothelial frequency range, Am – amplitude index of the myogenic frequency range, An – amplitude index of the neurogenic frequency range, Ar – amplitude index of the respiratory frequency range, Ac – amplitude index of the cardiac (heart) frequency range

Table 5. Results of univariate regression analysis of the haptoglobin concentration dependence on the amplitudes of the endothelial frequency range (Ae)

	b0	Standard error b_0	b_1	Standard error b_1	p
Ae	1787	190,362	-4053	1505	0,009

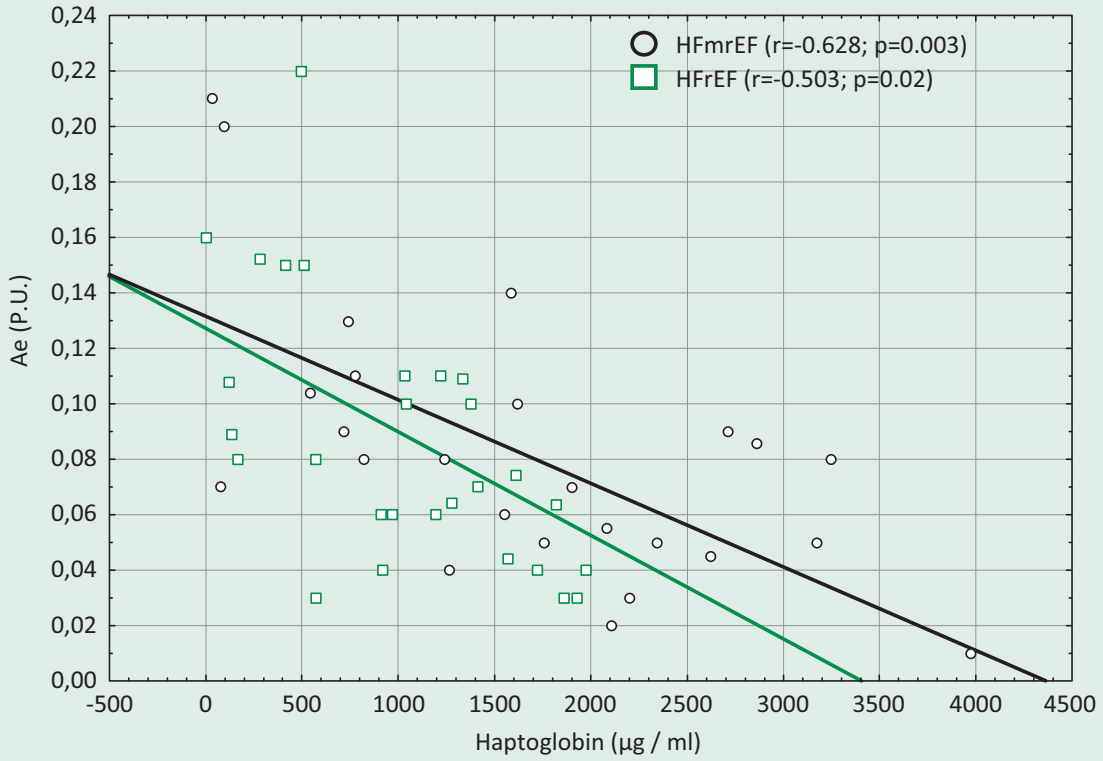
b_0 – constant, b_1 –regression coefficient, Ae – predictor value

associated with an increased risk myocardial infarction, stroke and CHF [19].

On the contrary, V. Haas et al. pointed out the unfavorable prognostic effect of low haptoglobin levels in patients with acute myocardial infarction [20]. Lu D.Y. et al. observed 41 patients hospitalized with acute decompensated heart failure, and they also showed that a decrease in the concentration of haptoglobin in blood plasma <177.1 ng/ml, due to its binding to myoglobin, was accompanied by a decrease in survival, especially when it's combined with more high NT-proBNP values [21]. None of our patients had such «extremely» low levels of plasma concentration of the studied antioxidant.

In our study, the lowest haptoglobin values were observed in patients with decreased LVEF, which in itself is a predictor of a poorer prognosis during CHF [1]. It's known that a decrease in the concentration of haptoglobin negatively affects its ability to implement antioxidant and anti-inflammatory functions [1,3,18]. This indirectly promotes the accumulation of reactive oxygen species in tissues, provokes the development of oxidative stress in cells and their release of «alarmine» interleukin-6, which causes vasoconstriction and promotes the progression of multiple organ manifestations of CHF [21]. Interleukin-6 induces the synthesis of haptoglobin, which realizes its antioxidant and anti-inflammatory activity not only by binding to toxic free hemoglobin, but also through the activation of T-helpers of types 1 and 2, due to which temporary compensation of the pathological process is achieved [22].

Therefore, we performed a linear univariate analysis, according to the results of which we obtained a statistically significant, moderately strong negative relationship between the haptoglobin levels and the amplitudes of the endothelial frequency range (Ae) in CHF patients with LVEF <50%. We have proposed a formula for the predicted value of the haptoglobin level depending on the level of amplitudes Ae. In our model, it is the endothelium that is a group of cells that starts a cascade of antioxidant reactions that play a protective role and slow down the progression of CHF.



Ae – the amplitude index of the endothelial frequency range, HFmrEF – heart failure with midrange ejection fraction, HFrEF – heart failure with a reduced ejection fraction

Figure 2. Correlation of haptoglobin levels and Ae in heart failure patients with intermediate and reduced left ventricular ejection fraction

It should be noted that myoglobin enters the bloodstream together with hemoglobin in acute myocardial damage or decompensation of CHF. Myoglobin is also highly toxic when free in blood plasma [23]. Free myoglobin competes with erythrocyte hemoglobin for binding to oxygen in the lungs and doesn't carry out the function of transferring oxygen to tissues, thereby impairing tissue oxygenation and leading to the development of tissue hypoxia, aggravating metabolic disorders in tissues [2,4,12,18]. Consequently, initially low concentrations of haptoglobin can't meet the body's needs for it, which leads to decompensation of the disease.

Our results are consistent with pathogenetic ideas about the function of haptoglobin in the body. For example, the minimum level of this protein, determined in the most clinically severe group of patients with HFrEF, may indicate the decompensation of processes associated with the depletion of antioxidant buffers in the body and high activity of systemic inflammation in patients with CHF [12, 19], and this also indicates dysfunction liver in the framework of the cardio-hepatic syndrome [24], one of the manifestations of the syndrome of multiple organ failure characteristic of the terminal stage of CHF [1].

Based on the data obtained on the absence of a relationship between the levels of haptoglobin and GFR and the degree of systolic dysfunction, it can be assumed that a decrease in cardiac output and in glomerular filtration rate are not the main factors leading to an increase in the plasma concentration of haptoglobin, both by stimulating its synthesis and by reducing excretion through the kidneys.

In our opinion, the revealed statistically significant negative relationship between the level of haptoglobin and Ae in the groups with reduced and intermediate EF indicates the induction of haptoglobin synthesis in response to the development and progression of endothelial dysfunction, diagnosed on the basis of a decrease in Ae amplitudes in patients with CHF when compared with the control group. Frimat M. et al. showed primary endothelial damage during overloading of antioxidant systems [25], which is

consistent with the data of M.M. Alem [26] and C. Zuchi et al. [27], postulating the dominant role of endothelial dysfunction in the pathogenesis of CHF and expressing the possibilities of its non-drug and pharmacological correction. Probably, patients with CHF have parallel activation processes of regulatory humoral systems and the formation of microvascular dysfunction, the subtle mechanisms of interaction of which require further study.

The data obtained by us on the preservation of the constancy of the microcirculation index even with significantly pronounced systolic dysfunction, including for HFrEF, seems to be very relevant. This indicates the importance of maintaining a constant blood flow in the microcirculatory bed for maintaining homeostasis both at the level of individual organs and tissues, and the whole organism as a whole.

The revealed negative relationship of haptoglobin with Kv and σ is a sign of an increase in the tension of regulatory systems and a decrease in the MC adaptation reserves with a decrease in the concentration of haptoglobin. In the HFmrEF group, the maximum value of the haptoglobin level is observed at the minimum value of Kv, which can tell us that the realization of its organoprotective function in these patients reaches maximum values and doesn't require active modulation of the MC to maintain tissue perfusion [26,28]. Rastogi A. et al. hypothesized that HFmrEF is heterogeneous and unstable, since patients can move to both the HFrEF group and the HFpEF group [29], and therefore patients with HFmrEF are in the «bifurcation point» with the highest tension of the compensatory systems of the body that determine their further forecast.

Conclusion

Thus, our results can complement our understanding of the pathophysiological role of haptoglobin during CHF. The revealed relationships between the haptoglobin level and the amplitude indices of the endothelial frequency range allow us to consider haptoglobin as one of the humoral mediators of the endothelial dysfunction progression in patients with CHF. We can assume that lower values of the plasma level of haptoglobin should be considered as a potential marker for the development of complications and used in a comprehensive assessment of the patients' prognosis, including for the diagnosis of the cardio-hepatic syndrome.

Evaluation of the haptoglobin diagnostic and prognostic significance, especially in patients with HFmrEF, requires further study, both in order to expand our understanding of the CHF pathogenesis and to search for new methods for correcting endothelial dysfunction and new approaches to the treatment of CHF.

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