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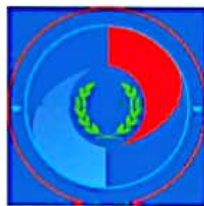
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ЗДРАВООХРАНЕНИЯ
РЕСПУБЛИКИ УЗБЕКИСТАН



САМАРКАНДСКИЙ
ГОСУДАРСТВЕННЫЙ
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ИННОВАЦИОННЫЕ ТЕХНОЛОГИИ В ЗДРАВООХРАНЕНИИ: НОВЫЕ ВОЗМОЖНОСТИ ДЛЯ ВНУТРЕННЕЙ МЕДИЦИНЫ

МАТЕРИАЛЫ

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Под редакцией
Ж.А. РИЗАЕВА


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ИЗУЧЕНИЕ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ У БОЛЬНЫХ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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АННОТАЦИЯ

Одним из основных факторов, определяющих прогноз у больных хронической сердечной недостаточностью (ХСН), является дисфункция эндотелия. Целью работы явилось определение антитромбогенной и вазодилатирующей активности сосудистой стенки у больных ХСН. Нами обследовано 70 человек, из которых 50 составили основную группу — больные с перенесенным Q-инфарктом миокарда и 20 человек — группа сравнения. Для определения антитромбогенных свойств стенки сосудов нами использована «манжеточная» проба. Сосудодвигательную функцию эндотелия изучали в пробах с реактивной гиперемией (РГ) и нитроглицерином (НТГ). У больных ХСН имеется снижение антитромбогенной и вазодилатирующей активности сосудистой стенки. У больных с IV ФК ХСН, имеющих большую продолжительность симптомов ХСН, $FW < 33\%$ число повторных неблагоприятных сердечно-сосудистых событий в течение 6 мес наблюдения достоверно больше по сравнению с пациентами I, II и III ФК ХСН.

Ключевые слова: хроническая сердечная недостаточность, эндотелиальная дисфункция.

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STUDY OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH CHRONIC HEART FAILURE

ANNOTATION

One of the factors defining prognosis in patients with heart failure (CHF) is endothelial dysfunction. The aim of the given study was to define antithrombogenic and vasolidating vascular wall activity in patients with CHF. 60 examined patients comprised two groups: the main group consisted of 40 patients after Q-myocardial infarction, the comparison group consisted of 20 patients. To determine antithrombogenic properties of vascular wall, «cuff testing» method developed by V.P.Balouda was used. Endothelial vasomotor function was studied using probes with reactive hyperemia and nitroglycerin. In patients with CHF decrease of antithrombogenic and vasolidating vascular wall activity was observed. During six months of monitoring the number of repeated unfavorable cardiovascular events in patients with IV functional class CHF having long term CHF symptoms and EF value $< 33\%$ is reliably higher in comparison with patients of I, II and III functional classes of CHF.

Keywords: chronic heart failure, endothelial dysfunction.

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SURUNKALI YURAK YETISHMOVCHILIGI BO'LGAN BEMORLARDA ENDOTELIAL DISFUNKTSIYANI O'RGANISH

ANNOTATSIYA

Surunkali yurak yetishmovchiligi (SYYe) bo'lgan bemorlarda prognozni belgilovchi asosiy omillardan biri endotelial disfunktsiyadir. Ishning maqsadi SYYe kasalliklarida qon tomir devorining antitrombogen va vazodilatatsion faolligini aniqlashdir. Biz 70 kishini tekshirdik, ulardan 50 asosiy guruhni tashkil etdi — Q-tishli miyokard infarkti bilan og'rigan bemorlar va 20 kishi-taqqoslash guruhi. Tomir devorining antitrombogen xususiyatlarini aniqlash uchun biz "manjet" namunasidan foydalanamiz. Endotelial vazomotor funktsiyasi reaktiv giperemiya va nitrogliserin bo'lgan namunalarda o'rganildi. SYYe kasalliklarida qon tomir devorining antitrombogen va vazodilatatsion faoligi kamayadi. SYYe IV FS bilan og'rigan bemorlarda, SYYe simptomlarining uzoq davom etishi bilan, FW<33% 6 oy davomida takroriy salbiy yurak-qon tomir voqealar soni SYYe I, II va III FK bemorlariga nisbatan ancha yuqori.

Kalit so'zlar: surunkali yurak yetishmovchiligi, endotelial disfunktsiya.

Relevance. The main factors that determine the prognosis are: CHF etiology, functional class (FC) of CHF, ejection fraction (EF), endothelial dysfunction [1]. When analyzing the prognosis of patients depending on the initial left ventricular EF, it was shown that the development of adverse cardiovascular events, including mortality, increases in parallel with a decrease in EF below 45%, while if this indicator is exceeded, the prognosis does not change at any value myocardial contractility [2, 3]. A decrease in the contractility of the left ventricular myocardium leads to the development of peripheral hemodynamic disorders, including the development of endothelial dysfunction [4]. The endothelium is not just a barrier between blood flow and vascular smooth muscle, but is also the site of formation of compounds involved in the regulation of blood coagulation, vascular tone, platelet function and development of the vascular wall [4, 5]. Narui development of adverse cardiovascular events, including fatal outcomes [6]. The aim of our study was to determine the antithrombogenic and vasodilating activity of the vascular wall in patients with impaired systolic function of the left ventricle that developed after a Q-myocardial infarction, and its role in the prognosis of CHF.

Material and research methods. 70 people were examined, of which 50 made up the main group — patients with Q-myocardial infarction and symptoms of chronic heart failure; 20 people were practically healthy individuals included in the comparison group. Inclusion criteria: 1) the presence of chronic heart failure of various functional classes (FC), which developed after Q-myocardial infarction, and the ejection fraction (EF) of the left ventricle is less than 45% [2]; 2) the patient's consent to participate in the study, confirmed by his signature in the protocol of observation. Exclusion criteria: 1) destabilization of coronary heart disease (unstable angina, recurrent myocardial infarction); 2) the presence of exacerbation of chronic processes at the time of the study.

Table 1

Clinical characteristics of patients with chronic heart failure

Indicators	All patients with CHF (n=50)	CHF I FC (n=10)	CHF II FC (n=15)	CHF III FC (n=15)	CHF IV FC (n=10)
Age, years	54.5±0.05	52.1±2.5	54.9±2.4	56.0±2.0	55.3±2.7
Men/women, %	85/15	80/20	90/10	90/10	80/20
Number of myocardial infarctions	1.2±0.09	1.2±0.1	1.2±0.1	1.3±0.2	1.4±0.3
Duration of manifestations of heart failure, years	5.30±2.3	2.1±0.6**	2.3±0.7**	2.0±0.7**	4.5±0.4**



Stable angina, %	97.5	one hundred	one hundred	one hundred	90
Arterial hypertension, %	85	70	90	80	one hundred
Duration of arterial hypertension, years	5.8±2.1	4.9±2.8	3.7±1.3	6.0±2.5	8.7±2.1
Diabetes, %	15	10	10	10	thirty
Atrial fibrillation, %	0.5	Not	Not	10	10
Smoking, %	60	15	15	15	15
Distance of 6-minute walk, m	319.3±24.3	506.5±6.7*	411.5±12.2*	257.0±12.1*	112.0±16.6*

Note: * $p < 0.01$ — significance of differences between the groups of patients with CHF I FC, CHF II FC, CHF III FC and CHF IV FC.

The examination was carried out one week after stabilization of the patient's condition. Characteristics of patients with chronic heart failure is presented in Table. 1. The average age of the examined patients is 54.5 years (from 42 to 70 years); men predominated - 34 (85%) people; the average number of myocardial infarctions 1.2; the duration of manifestations of heart failure in the group was 5.3 years; most patients had symptoms of stable functional class III angina - 97.5% of people, 85% of patients had arterial hypertension, the duration of the increase in blood pressure for 5.8 years, 6 (15%) people had type II diabetes mellitus, 2 (0.5%) of patients had a permanent form of atrial fibrillation, more than half of the examined - 24 (60%) people smoked; the distance of a 6-minute walk was 319.25 m. All patients, depending on the results of the 6-minute test, were divided into four functional classes, the significance of differences between groups was $p < 0.01$. As can be seen from Table. 1, there were no significant differences between patients with different FCs in the studied characteristics, with the exception of the duration of manifestations of heart failure. In patients with FC IV, symptoms of CHF were significantly ($p < 0.01$) recorded for a longer time than in patients with other functional classes.

The study of systolic function of the left ventricular myocardium and indicators of remodeling of the heart was carried out on the device "Apogee CX" using a sensor with a frequency of 2.75 MHz with simultaneous recording of a two-dimensional echocardiogram and Doppler echocardiogram in a pulsed mode.

To determine the antithrombogenic (anticoagulant and fibrinolytic) properties of the vascular wall, we used a "cuff" test based on the creation of short-term (within 5 minutes) ischemia by applying a sphygmomanometer cuff to the patient's shoulder and creating a pressure of 30 mm Hg in it. Art. higher than systolic, proposed by V.P. Baludoy et al. [7]. At the same time, prostacyclin, antithrombin III and plasminogen activator are released from the vessels into the blood. The difference in the content or activity of these factors in the blood taken before and after the cuff test is used to judge the state of antithrombogenic activity. Antithrombin III accounts for more than 80% of all anticoagulant activity. Based on the results of determining the activity of antithrombin III in plasma obtained before and after the "cuff" test, the anticoagulant activity of the vessel wall is judged.

The determination of the fibrinolytic activity of the vessel wall is based on the fact of accelerating the lysis of euglobulins obtained from platelet-poor plasma treated with kaolin [7]. Euglobulin fraction containing plasminogen, fibrinogen and blood coagulation factors and not containing fibrinolysis inhibitors is isolated from blood plasma. When calcium chloride is added, a fibrin clot is formed, which is lysed by plasmin in 5-12 minutes. Endothelial cells are capable of synthesizing tissue-type plasminogen activator. The fibrinolytic activity of the vessel wall was characterized by an index equal to the division of the time of euglobulin clot lysis after the cuff test to the time of euglobulin clot lysis before it. The time of clot lysis after clamping is normally shortened by 1.5-2 times. The weakening of the activation of euglobulin fibrinolysis is a marker of endothelial damage. For this study, reagent kits from NPO Renam were used. The vasomotor function of the endothelium was studied in samples with reactive hyperemia (HR) and



nitroglycerin (NTG) [8]. On the day of the study, the patients did not smoke or take any medications. The patient was lying on his back for at least 10 minutes prior to the start of the study. To image the right brachial artery (BA), measure its diameter and blood flow velocity, we used an ACUSON 128 XP/10 system equipped with a 7 MHz phased array linear transducer. The vasomotor function of the endothelium was studied in samples with reactive hyperemia (HR) and nitroglycerin (NTG) [8]. On the day of the study, the patients did not smoke or take any medications. The patient was lying on his back for at least 10 minutes prior to the start of the study. To image the right brachial artery (BA), measure its diameter and blood flow velocity, we used an ACUSON 128 XP/10 system equipped with a 7 MHz phased array linear transducer. The vasomotor function of the endothelium was studied in samples with reactive hyperemia (HR) and nitroglycerin (NTG) [8]. On the day of the study, the patients did not smoke or take any medications. The patient was lying on his back for at least 10 minutes prior to the start of the study. To image the right brachial artery (BA), measure its diameter and blood flow velocity, we used an ACUSON 128 XP/10 system equipped with a 7 MHz phased array linear transducer.

The VA diameter is measured at a fixed distance from the anatomical markers using ultrasonic gauges. Changes in blood flow velocity in RG are evaluated as a percentage of the initial value. A normal reaction of PA is considered to be its expansion against the background of reactive hyperemia by 10% or more of its initial diameter [8, 9]. A lesser degree of vasodilation, or vasoconstriction, is considered a pathological reaction.

Statistical processing was performed using the STATISTIKA 5.5 statistical software package. Among the processing methods, simple statistics, Student's t-test were used. The difference between the studied parameters was recognized as significant at $p < 0.01$.

Research results. We found a significant decrease in the ejection fraction (EF) ($p < 0.01$) in all groups of patients compared with healthy individuals. EF in patients with I, II, III FC CHF were comparable and amounted to 40%. There was a significant ($p < 0.01$) decrease in EF (33%) in patients with FC IV compared with patients of other groups. Patients with CHF significantly ($p < 0.01$) have more ESR of the left atrium (LA), EFR, EDR, ESR and ELV of the left ventricle (LV); thickness of the anterior wall of the right ventricle, KDR of the pancreas; systolic pressure of the pulmonary artery (SPPA) in comparison with similar indicators of the comparison group. At the same time, LA EFR and LV EDR, SPPA in patients with FC IV are significantly higher ($p < 0.01$) compared with patients with FC I, II, III CHF. The thickness of the interventricular septum and the posterior wall of the left ventricle in patients with CHF were comparable and significantly ($p < 0.01$) greater than in healthy individuals. Diastolic function in all patients with CHF is impaired by a restrictive type. The LV myocardial mass index in all patients with CHF was significantly ($p < 0.01$) higher than in the comparison group. Two patients with FC IV CHF had thrombi in the LV cavity.

Table number 2

Indicators of systolic dysfunction and myocardial remodeling in patients with chronic heart failure (M±m)

Indicators	Comparison group (n=20)	CHF I FC (n=10)	CHF II FC (n=15)	CHF III FC (n=15)	CHF IV FC (n=10)
Left ventricular ejection fraction, %	64.3±0.9*	40.5±1.4	40.2±3.0	40.4±3.0	33.1±2.0 ^{1 2 3}
CSR of the left atrium, cm	3.5±0.1*	4.2±0.1	4.2±0.2	4.48±0.1	5.03±0.2 ^{1 2 3}
CSR of the left ventricle, cm	3.21±0.1*	4.6±0.1	4.5±0.3	4.7±0.3	5.4±0.4
KDR of the left ventricle, cm	4.9±0.1*	6.0±0.1	5.9±0.2	6.0±0.2	6.8±0.3 ^{1 2 3}
CSR of the left ventricle, ml	41.9±1.9*	109.1±8.2	110.3±8.8	114.8±15.4	131.7±14.9
EDV of the left ventricle, ml	117.9±5.1*	190.6±10.0	196.4±18.0	195.7±18.6	202.9±20.2
TMZhP, cm	0.99±0.02*	1.20±0.09	1.1±0.06	1.1±0.10	1.2±0.09



Type of diastolic dysfunction	E/A<1.6	E/A>2	E/A>2	E/A>2	E/A>2
Presence of thrombi in the LV cavity, pers.	—	—	—	—	2 (20%)

Note: * $p<0.01$ — significance of differences between the comparison group and patients with CHF of FC I, FC II, FC III, FC IV;

Thus, in all patients with LV systolic dysfunction, processes of remodeling of both the left and right parts of the heart occur. In patients with FC I, II, III CHF, with comparable EF, there are no significant differences in the parameters of heart remodeling. In patients with CHF FC IV, who have a longer duration of manifestations of heart failure, lower EF, remodeling indices - LA EFR, LV EDR and SPPA - are significantly higher ($p<0.01$) compared with patients with FC I, II, III CHF.

We have evaluated the antithrombogenic (anticoagulant and fibrinolytic) activity of the vascular wall in patients with CHF. In the examined patients with CHF, initially there were no changes in the activity of antithrombin III before the test with PA occlusion. The activity of antithrombin III after the test in patients with CHF is reduced, but with this number of patients it does not reach the degree of reliability ($p>0.01$). A significant ($p<0.01$) decrease in the anticoagulant activity of the vascular wall was found in patients with II, III and IV FC CHF compared with healthy individuals.

Table number 3

Indicators of anticoagulant and fibrinolytic activity of the vascular wall in patients with chronic heart failure (M±m)

Indicators	Comparison group (n=20)	CHF I FC (n=10)	CHF II FC (n=15)	CHF III FC (n=15)	CHF IV FC (n=10)
Antithrombin III activity before the cuff test, %	91.6±3.9	92.5±2.4	92.2±2.2	90.1±1.2	90.0±2.9
Antithrombin III activity after cuff test, %	98.8±4.3	91.2±2.5	92.0±2.2	91.0±1.6	92.7±2.7
Anticoagulant activity of the vascular wall, arb. units	1.14±0.02	0.98±0.13	0.99±0.01*	1.01±0.01*	1.02±0.01*
Fibrinolysis time before cuff test	8.4±0.43	8.4±0.7	8.8±0.5	9.8±1.6	12.3±1.5*
Fibrinolysis time after cuff test	7.6±0.44	8.0±0.6	8.6±0.4	10.0±1.7	11.5±1.4* $p<0.05$
Fibrinolytic activity of the vascular wall, arb. units	1.12±0.06	0.95±0.19	0.97±0.01*	1.02±0.01*	0.94±0.02*

Note:

* $p<0.01$ — significance of differences in the time of fibrinolysis before and after the cuff test between the comparison group and patients with CHF IV FC;

When studying the fibrinolytic activity of the blood, it was revealed that the time of fibrinolysis before and after the cuff test tends to increase as the functional class of CHF increases and becomes significantly higher ($p<0.01$) in patients with FC IV CHF compared with persons in the comparison group. A pronounced decrease in the fibrinolytic activity of the vascular wall was found in patients with II, III and IV FC CHF compared with the same parameter in healthy individuals ($p<0.01$).

Anticoagulant and fibrinolytic activity of the vascular wall in patients with FC I CHF is comparable to healthy individuals. In patients with FC I CHF, who have systolic myocardial dysfunction, the

antithrombotic activity of the vascular wall is not changed, which is associated with the work of neurohumoral systems and causes compensation for heart failure in these patients. In patients with II, III, IV FC CHF, the anticoagulant and fibrinolytic activity of the vascular wall is reduced. Depression of the fibrinolytic system was revealed in patients with FC IV CHF, which is an important condition for the formation of blood clots in the vascular bed [10].

The vasomotor function of the endothelium in patients with various functional classes of CHF was studied in samples with reactive hyperemia (HR) and nitroglycerin (NTG) [8, 9]. Data on the parameters of the study of the brachial artery (BA) in patients with various functional classes of CHF are given in Table. 4.

Table 4

Parameters of the study of the brachial artery in patients with chronic heart failure with different functional classes (M±m)

Indicators	Comparison group (n=20)	CHF I FC (n=10)	CHF II FC (n=15)	CHF III FC (n=15)	CHF IV FC (n=10)
Initial diameter of PA, mm	3.6±0.05	4.9±0.09*	4.7±0.32*	4.8±0.18*	4.6±0.4*
Initial blood flow velocity, m/s	0.7±0.03	0.5±0.03*	0.5±0.03*	0.5±0.02*	0.5±0.03*
PA diameter at the 60th sec in the sample with RG	4.1±0.08	5.3±0.14*	5.1±0.26*	5.3±0.10*	4.95±0.30*
PA diameter at the 5th minute in the sample with NTG	4.2±0.07	5.4±0.18*	5.33±0.23*	5.42±0.23*	5.4±0.4*
Flow-dependent dilatation at 60 sec, %	16.3±0.76	6.3±1.1*	8.1±2.1*	9.1±2.6*	6.3±2.4*
NTG-induced dilatation, %	20.8±1.5	7.5±1.7*	13.6±2.9*	13.4±2.7*	14.7±2.3*
Reactive hyperemia, % increase in speed	14.8±1.2	26.5±6.1	24.1±5.6	13.5±6.6	13.1±4.6

Note: * p<0.01 — significance of differences between the comparison group and patients with CHF I FC, CHF II FC, CHF III FC and CHF IV FC;

We found a significant increase in the initial diameter of the VA (p<0.01) and a decrease in the initial blood flow velocity (p<0.01) in patients with I, II, III, IV FC CHF in comparison with similar indicators in the comparison group. We have not found significant differences in the initial VA diameter and the initial blood flow velocity in CHF patients with different functional classes. During the test with reactive hyperemia, a significant increase in the initial diameter of the brachial artery (p<0.01) was noted in patients with all FC CHF in comparison with the comparison group. According to the literature, flow-induced dilatation is inversely proportional to vessel diameter, and in arteries with a diameter of 6 mm, the less than average vessel dilatation is 10%. Its lower value, or vasoconstriction, is considered pathological [8]. Flow-dependent dilatation at the 60th second in patients with CHF is significantly lower (p<0.01) than in healthy individuals and amounts to 6.3% in FC I, 8.1% in FC II, and 9 in FC III. .1%, with IV FC - 6.3%, which is pathological. In one patient with CHF I FC, one patient with CHF II FC and two patients with CHF IV FC (10%), the diameter of the brachial artery did not change at the 60th second of the "cuff" test. Thus, in patients with CHF and impaired systolic function of the left ventricle, there are initial disturbances in the tone of the brachial artery and blood flow velocity in it. In all patients with CHF, disorders of endothelium-dependent vasodilation were revealed. In 10% of patients with CHF, there was no endothelium-dependent vasodilation on the action of endogenous stimuli. Insufficient vasodilation in patients with CHF I and II FC leads to an increase in reactive hyperemia (% increase in rate),



Thus, in patients with FC I, II, III, IV CHF and impaired systolic function of the left ventricle, there are violations of vascular tone in the form of an increase in diameter and a decrease in blood flow velocity in the VA. In response to endogenous stimulation, there is no sufficient relaxation of PA, and in 10% of those with CHF, vascular tone does not change, which indicates a violation of endothelium-dependent vasodilation. In patients with FC I, II, III, IV CHF and systolic dysfunction of the myocardium, violations of endothelium-independent vasodilation were also detected, but to a lesser extent.

Discussion. A decrease in cardiac output is accompanied by a violation of peripheral hemodynamics in the form of a decrease in blood flow velocity and, probably, compensatory vasodilation of the brachial artery. Systolic dysfunction of the LV myocardium in patients with FC I, II, III, IV CHF is accompanied by a violation of the vasomotor function of the endothelium, the causes are both insufficient synthesis of vasodilation factors (nitric oxide, endothelial hyperpolarizing factor, prostacyclin) and excessive formation of vasoconstrictors (angiotensin II, endothelin, free radicals of under oxidized fatty acids, prostaglandin F_{2α} and thromboxane A₂). We analyzed the adverse cardiovascular events that developed within 6 months in the examined patients on the background of standard therapy with ACE inhibitors, β-blockers, diuretics, aldosterone antagonists, nitrates, antiplatelet agents, statins in optimal doses for each patient. Patients with reduced LV systolic function, I and II FC CHF did not develop adverse cardiovascular events during 6 months of follow-up. One patient with FC III CHF developed recurrent myocardial infarction. In half (50%) of patients with FC IV CHF and a significantly reduced LV ejection fraction, the following adverse cardiovascular events were recorded during 6 months of follow-up: one patient developed unstable angina, four patients developed decompensated CHF, one person died.

Conclusions. Violation of the systolic function of the left ventricle in patients with I, II, III and IV FC CHF who underwent Q-myocardial infarction is accompanied by a decrease in the antithrombogenic and vasodilating activity of the vascular wall. In patients with reduced systolic function of the left ventricle and FC I CHF, there were no violations of the antithrombogenic activity of the vascular wall. There were no significant differences in the severity of endothelial dysfunction in patients with I, II, III, and IV FC CHF who underwent Q-myocardial infarction. In patients with CHF FC IV, who have a longer duration of CHF symptoms, EF 33% or less, the number of recurrent adverse cardiovascular events during 6 months of follow-up is significantly higher compared to patients with CHF FC I, II and III.

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