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Early Diagnosis of Endothelial Dysfunction in Patients with Chronic Heart Failure

Kamilova U. K.[1,*], Shoalimova Z. M.[2], Avezov D. K.[2]

[1]Specialized Scientific-Practical Medical Center of Therapy and Medical Rehabilitation, Tashkent, Uzbekistan
[2]Tashkent Medical Academic, Tashkent, Uzbekistan

Abstract The aim of the research was to examine the endothelial dysfunction and to develop the criteria for early diagnosis of CHF. We examined 273 patients, men with postinfarction cardiosclerosis, complicated by heart failure at the age of 40 to 60 years (average age of 53,3 ± 4,9 years). The survey included patients after myocardial infarction with prescription from 6 months to 3 years. All patients underwent an electrocardiogram, the full complex of clinical and biochemical examinations. Besides, patients were assessed by Six-minute walking test, echocar-diography an initial and after 3 and 6 months of the treatment. Endothelial function was estimated by brachial artery Doppler procedure by applying reactive hyperemia. The outcomes evaluated by the following parameters. In patients of CHF the process of left ventricular remodeling associated with vascular remodeling caused by endothelial dysfunction. Endothelial dysfunction in patients with CHF is associated with the progression of the disease and is characterized by decreased of endothelium-dependent vasodilation (EDV), severe paradoxical vasoconstriction, significant reduction in velocity parameters, increased secretion of humoral markers of endothelial dysfunction - von Willebrand factor.

Keywords Chronic heart failure, Endothelial dysfunction, Willebrand factor

1. Introduction

Chronic heart failure (CHF) is not only a medical but also a social challenge due to significant prevalence, high mortality rates. According to the Framingham Heart Study, conducted at Boston University School of Medicine, one of the leading causes of heart failure is coronary heart disease (CHD), which is more than 60% in the structure of CHF development. This pathology sharply worsens the quality of life of patients and increases the risk of death in 4 times: it can vary from 15 to 50% during a year. The risk of sudden death in patients with CHF is 5 times higher than in those without heart failure. About 50% of patients with CHF, despite the use of combination therapy, die within 5 years after the onset of clinical symptoms. The chronic heart failure (CHF) remains to be one of the most important problems of a modern cardiology owing to a wide circulation and the adverse forecast, despite the significant progress in optimization of its treatment. The urgency of the studied problem is caused by CHF wide incidence universally and among cardiovascular diseases (CVD). The disease sharply worsens the life quality of patients, increases the risk of lethality by 4 times, and death rate of patients within a year makes 15-50%.

Currently, endothelium dysfunction (ED) plays the significant role in CHF pathogenesis along with disturbances of neurohumoral regulation - activation of the sympathetic-adrenal system (SAS) and the renin-angiotensin-aldosterone systems (RAAS). The leading pathogenetic role in the development and advances of CHF belongs to oppression of endothelium synthesis - the produced nitrogen oxide (NO). Oppression of NO synthesis is considered as one of the main pathogenetic mechanisms. ED can be primary, genetically determined and at the same time the important part is assigned to genes which are responsible for synthesis of nitrogen oxide (NO) of endothelial NO synthase (eNOS) which is enzyme responsible in regulation of the tonus of blood vessels, work of smooth muscle musculation of vascular wall and processes of thrombogenesis by endothelium.

The aim of the research: to examine the endothelial dysfunction and to develop the criteria for early diagnosis of CHF.

2. Material and Methods

We examined 273 patients, men with postinfarction cardiosclerosis, complicated by heart failure at the age of 40 to 60 years (average age of 53,3 ± 4,9 years). The survey

* Corresponding author:
umida_kamilova@mail.ru (Kamilova U. K.)
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included patients after myocardial infarction with prescription from 6 months to 3 years. All of the patients were hospitalized in the cardiology department of the clinic 1 Tashkent Medical Academy.

Patients were randomized into groups by CHF functional class (FC) according to the classification of the New York Heart Association according to the six-minute walk test (SMWT) and on a scale clinical condition (SCC) patients. Group of patients with FC I comprised 44 patients, the average age were 56,2 ± 4,8 years, myocardial infarction (MI) prescription was 2,1±0,6 years. FC II patients were 113 people at average age 53,8±4,1 years, with MI prescription 2,4±1,0 years and FC III - 116 patients at average age 52,3±3,8 years, MI prescription was 2,0±0,5 years. To compare the data surveyed a group of healthy individuals (control group) consisting of 31 people matched by sex, age with the main group. The examination did not include the patients with insult, diabetes mellitus, chronic obstructive pulmonary disease, severe arrhythmia, hepatic diseases.

All patients underwent an electrocardiogram, the full complex of clinical and biochemical examinations. Besides, patients were assessed by Six-minute walking test, echocardiography an initial and after 3 and 6 months of the treatment. Endothelial function was estimated by brachial artery (BA) Doppler procedure by applying reactive hyperemia (RH) and nitroglycerin tests. The outcomes evaluated by the following parameters: frequency of readmissions, the incidence of complications, the incidence of fatal and nonfatal myocardial infarction and mortality.

The structure of the basic therapy was as follows: 71% received ACE inhibitor patients, Angiotensin receptor antagonists - 23% of patients, a diuretic - 46% (furosemide), spironolactone - 58%, digoxin - 11%, aspirin - 85%, long-acting nitrates - 28%, statins - 62%. To assess the dynamics of the studied parameters during long-term therapy with beta-blockers, patients were divided into 2 groups: in 1st group- 120 patients who received cardioselective beta-blocker - bisoprolol in the complex treatment, in 2nd group- 153 patients who received nonselective, having α1 blocked property beta-blocker – carvedilol.

The diagnosis was based on clinical and laboratory research tool. In the survey did not include patients with acute disorders of cerebral circulation, diabetes, COPD and complex arrhythmias that was initially excluded by Holter ECG monitoring, in the absence of cardiac arrhythmias patients were included in the study.

Statistical data processing. Data obtained in the study were subjected to statistical processing on a PC Pentium-IV using the software package Microsoft Office Excel-2012, including the use of built-in functions of the aggregation. For statistically significant changes have taken confidence level P <0,05. Statistical significance for qualitative variables was calculated using the $\chi 2$ criterion (chi-square) and the z-criterion (Glanz). For dependency analysis features calculated the Pearson correlation coefficient of pair (r).

3. Results

Indicators of exercise tolerance in patients examined in patients with CHF FC I made based on the results of SMWT were 417,4 ± 17,89 meters. Patients with CHF FC II and III showed a decrease in exercise tolerance by 18% and 44% as compared with the patients with CHF SMWT FC I, representing 346,1 ± 19,25 and 237,9 ± 20,55 meters, respectively.

Baseline values of SCC in the patients with CHF FC I made 4,4±1,33 points, respectively. In patients with heart failure class II worsened clinical status of patients with increased performance SCC by 25% compared with patients with CHF of I FC SCC (P <0,001), accounting for 5,5±0,70 points, respectively. In patients with CHF FC III, this indicator was – 8,4±0,83 points, or 90% higher compared to SCC in patients with CHF FC I.

The study of indicators of endothelial dysfunction assested at results of vasomotor reaction in HA by Doppler found that in patients with FC I CHF endothelium-dependent vasodilation (EDV) violations occured in 56%, abnormal vasoconstriction in 12% of patients and 32% of patients had preserved endothelial function. In class II heart failure was observed a decrease in 2 times of the number of patients with preserved EDV, accounting for 13%, and patients with impaired EDV were 64%. In patients with FC III EDV violation was observed in 71%, abnormal vasoconstriction in 26% of patients (Figure 1).

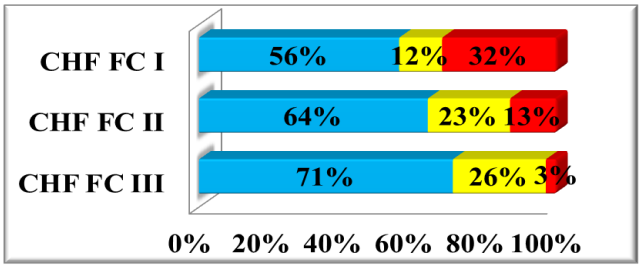

Figure 1. Baseline Doppler indexes reactive hyperemia in patients with I-III FC of CHF

Indicators of endothelial dysfunction were assessed by brachial artery vasomotor reaction showed that the progression of heart failure authentically reduced the rate of blood flow (Table 1).

In patients with FC I CHF, systolic and diastolic blood flow velocity (Vs) and (Vd) in brachial artery initially was lower by 19,5 and 31,2%, respectively, compared with the control group. Initial level average blood flow velocity was 46,7±1,08 cm/s versus 60,8±3,59 cm/s i.e by 23,2% was lower from the control group (CG) data.

In patients with FC I CHF at rest diameter of brachial artery 0,43±0,023 cm in the first group and 0,42±0,027 cm in the second group, respectively, versus 0,41±0,02 cm in healthy individuals. In patients with I FC CHF, brachial artery diameter was smaller compared to the control group of 4,8%.

Table 1. Initial state of blood flow in the brachial artery in patients with I-III FC CHF (M ± m)

Data	Control group	FC I	FC II	FC III
D_0 ,sm	0,41±0,02	0,43±0,01	0,38±0,015	0,33±0,003***
D_1 ,sm	0,45±0,02	0,47±0,01	0,41±0,016	0,34±0,005***
Vs ,sm/s	92,14±3,77	74,4±2,03***	67,1±1,84***	66,3±2,96***
Vd, sm/s	29,43±3,85	19,0±0,61*	14,8±1,68**	11,2±0,26***
Vm, sm/s	6,79±3,59	46,7±1,08**	41.0±1,02***	38,8±1,15***
Ri, r.unit	0,68±0,03	0,74±0,01	0,78±0,01**	0,83±0,005***
Pi, r.unit	1.04±0.07	1,19±0,03	1,28±0,01**	1,42±0,014***
EDV,%	14,8±2,4	14,0±0,72	12,0±0,99	12,8±1,49
τ_0, din/sm²	29,8±1,91	28,1±0,50	31,1±1,43	28,8±1,54
τ_1, din/ sm²	54,18±4,04	53,9±1,03	54,7±2,0	59,9±1,32
K, con. unit.	0,14±0,03	0,10±0,004	0,08±0,004	0,05±0,013*

Note: * - the differences are authentic with respect to the Control group data (* - P<0.05, ** - P<0.01, *** - P<0.001)

BA diameter changes at RH in the control group goes the growth of diameter of the vessel, unlike the patients with CHF, who have had the decrease of the diameter of vessel after the compression sample. In patients with CHF in response to increased blood flow on the 125,4±5,1 cm/s, the diameter of the BA increased by 8,7±1,0 versus 11,4±1,76% in healthy individuals. EDV in the control group was 11,4 ± 1,7%, and in patients with FC I showed a decrease of this index by 23,6 compared with the control group. Pulsatility index (Pi) initially in patients with FC I CHF exceeded control to 14.4%, and resistive index (Ri) 8,8%, respectively.

Considering the complexity of comparing indicators of endothelial function, we calculated the sensitivity of the BA to the change of the mechanical stimulus - the shear stress on the endothelium. Shear stress was measured before and after sample RH (τ_0 и τ_1). In both groups τ_0 was unauthentically different from controls, and τ_1 was significantly lower by 7% against CG. With regard to the sensitivity of the BA to shear stress, i.e. BA ability to vasodilatation but in patients with I CHF FC it was authentically lower than in control by 28,6%.

Diameter of BA at FC II CHF decreased by 7,3% of control. It was observed a decrease of systolic blood flow Vs in the BA by 27,4%, and Vd by 49,7% (P <0,01), respectively, compared with the control group. The average blood flow velocity in patients with first and second group FC II CHF was reduced by 32,6% compared with the data of healthy individuals. Study of initial indicators of Ri and Pi revealed that in patients with FC II heart failure, the figure was authentically higher on 14,7% and 23,3% respectively, compared with the control group (P<0,01). The analysis of the studied parameters after RH showed that the diameter of the BA in the control group increased by 11,4±1,76%, whereas in patients with CHF in response to increased flow velocity on 117,8±6,4 cm/diameter increased BA on the 7,2±1,1%. In RH phase in patients with CHF it was marked an increase in the diameter of the BA to 0,41±0,049 vs. cm to 0,45±0,02 in healthy individuals. The indicators of EDV in patients with class II heart failure were authentically lower on 37.8 (P<0,001), compared with the values of the control group. Initial level of τ_0 and τ_1 was 30,1±4,5 dyne/cm² and 53.7±6,3 dyne/cm² respectively, versus 29,8±1,91 and 54,2±4,04 dyne/cm² in healthy individuals. Initial indicator of BA sensitivity to shear stress in patients with FC II heart failure was reduced by 29,8% of the control group, respectively.

In the patients with FC III CHF in both groups found serious violation of EDV indicating a sharp deterioration of endothelial function: its decrease was observed in 68% of patients, pathological vasoconstriction in 30%, and only 2% of patients remained EDV of BA. An authentic decrease of systolic blood flow velocity by 29.2%, diastolic 62.1% (P<0.01) than in the control, respectively. It was noted decrease in average blood flow velocity in patients with FC III CHF 36,6% compared with the data of healthy individuals, making 38,9±1,80 cm/s, respectively. And the BA diameter was lower by 18,9%. Reduced EDV was 5,1±4,0%, respectively, against 11,4±1,7%, i.e. showed a decrease of this index by 56.5% compared with the control group (P<0,001). The analysis of resistance and pulsatility indicators showed that in patients with FC III CHF, these figures were higher than the control group by 37,4 and 31,2% (P<0,01), respectively. The decrease of the sensitivity of BA to shear stress was 64,3% (P<0.001) relative to the control groups.

On estimation the relationship between the degree of manifestation of endothelial dysfunction and CHF severity, we established that all patients with CHF presented endothelial dysfunction, herewith its severity was being increased at CHF progression.

One of the manifestations of endothelial dysfunction is disturbance of a vascular and platelet homeostasis. One of the humoral markers characterizing function of an endothelium is functional activity of thrombocytes. According to many researches data at CHF patients there is observed a rising of indicators of aggregation activity of thrombocytes. Study of functional activity of thrombocytes in the CHF FC I patients showed that the indicator of the aggregation activity of thrombocytes (AAT) was

authentically 2,4 times lower, than in healthy people, making 2,9±0,73 mkmole of ADP against 4,83±0,32 mkmole. The indicator of rate of aggregation of thrombocytes (Vagr) was 1,49±0,42 cm/min against 0,44±0,5 cm/min (P<0.001) in healthy people, i.e. it was a reliable rising of rate of aggregation by 3.4 times in comparison with an indicator of control group. The maximum amplitude of aggregation (Amax) was also authentically 2,1 times higher than at healthy people and was 1,91±0,45 cm against 0,9±0,17 cm (P<0,01). Patients from the II FC CHF had more expressed depression of an indicator of AAT - on 52,4 in comparison with group of healthy people. Vagr was increased by 4,5 times than indicators of control group (P<0,01), making 1,98±0,23 cm/min against 0,44±0,5 cm/min. Also Amax of aggregation was increased by 5 times (P<0,01) and was 2,96±0,43 cm against 0,9±0,17 cm at healthy people.

Development of CHF promoted more expressed change of the studied indicators: at CHF FC III of the AAT index was 3,2 times (P <0,001) lower from control that made 1,9±0,76 mkmole of ADP at patients respectively. The decrease of indicators of Vagr and Amax was 5 and 7 times (P <0,001) higher respectively in comparison with indicators of healthy people.

In intensifying of processes of aggregation of thrombocytes the important part is assigned to VWF which is contained in subendotheliums and under the influence of which fast activization of thrombocytes occurs, those changing the form, bulking up and forming aculeiform processes, adhere to fibers of a connecting tissue. Now VWF is considered as an early marker of dysfunction of an endothelium and has important prognostic value at CHF patients.

Its initial level in patients with FC I CHF was higher than the control on the 127,5%, accounting for 125,6 ± 5,30% respectively versus 112 ± 13,9% in healthy individuals. In patients with heart failure FC II was marked an authentic increase of the level of Von Willebrand factor (vWF), as compared with the control group by 42,2% with FC I on 26,8% amounting to 159,3±3,26% respectively.

In the patients with FC III CHF same figure was authentically higher by 53,5% (P<0,001) than in the control group, representing 172,8 ± 5,30 %. Consequently, the level of vWF determined in the blood plasma of patients with CHF, depending on the degree of functional class, its greatest value is observed in patients with FC III.

Thus, we found that in patients with FC I-III CHF is impaired endothelial function. This is reflected with decreasing of EDV, blood flow velocity parameters, paradoxical vasoconstriction, decreased sensitivity to endothelial shear stress, as well as an increase of vascular tone, platelet aggregation and vWF levels in plasma.

Monitoring function and humoral markers of endothelial dysfunction in patients CHF complicated by heart failure during long-term therapy. Study of indicators of endothelial dysfunction in patients with CHF surveyed showed that patients FC I CHF on a background of complex treatment with bisoprolol in 6 months BA diameter increased by 4.6%, Vs and Vd - 3.6% and 10.5% (P<0.05), mean flow velocity - 5% (P<0.05) and the index EDV - 18.4% (P<0.01). EDV decreased by 14.2%, resistive index of 1.35% (P<0.05) and pulsatility index of 4.2% (P<0.05). In the bisoprolol group after 6 months of therapy, the shear stress at rest and after RH increased by 3.1 and 1.1% from baseline values, and the sensitivity of the BA - by 11,1% (P<0.05). Carvedilol improved the studied parameters is more pronounced. By the end of therapy diameter of BA increased by 6% (P<0.001), and its dimensions are at rest and after WG increased by 8,3% and 13% (P <0.001) compared to baseline. Systolic and diastolic blood flow velocity increased by 12.8 and 55% (P<0.001), mean flow velocity by 21.1% (P<0.001) and index EDV - 38.8% (P<0.05). Resistive and pulsatility indices declined by 12,9 and 25,2% (P<0.001). EIDV decreased by 25.9% (P<0.001). The shear stress is at rest and after WG tended to increase sensitivity BA by 40% (P<0.05) from baseline. In patients with FC II CHF at 6 months bisopro-lol observed mean blood flow velocity and the diameter of the BA at rest ex-ceeded baseline by 3.6% and 4.1% (P<0.05). Also there was a significant in-crease EIDV 11.1% (P<0.05) compared with the original data.

Vs and Vd blood flow velocity increased by 12.8 and 55% (P<0.001), mean blood flow velocity by 21.1% (P<0.001) and index EDV - 38.8% (P<0.05). Resistive and pulsatility indices declined by 11.8 and 17.88% (P<0.001). EDV decreased by 25.9% (P<0.001). The shear stress is at rest and after WG tended to increase sensitivity BA by 40% (P<0.05) from baseline. In patients with CHF FC II at 6 months. bisoprolol observed mean blood flow ve-locity and the diameter of the BA at rest exceeded baseline by 3.6% and 4.1% (P<0.05). Also there was a significant increase EDV 11.1% (P <0.05) com-pared with the original data. Bisoprolol course positively affected the indica-tors of endothelial dysfunction in patients with CHF FC III. BA diameter in-creased by 6% (P<0.01) and after WG - 5.6 and 8.3% (P<0.01) from baseline values. EDV tended to increase by 34%, and the systolic and diastolic flow velocity of 2.7 and 15.2% (P<0.01), its average speed - 4.6% (P<0.05). Resis-tive and pulsatility indices declined by 2.4 and 4.2% (P<0.01). Shear stress at rest and after WG significantly increased - by 10.1 and 1.5% of the original da-ta, which was accompanied by a tendency to improve the sensitivity of the BA to shear stress.

Long-term therapy with carvedilol significantly improved indicators of endothelial function in FC III CHF patients. Diameter BA at rest increased by 8.8% (P<0.01) from baseline. Systolic, diastolic and mean blood flow velocity increased by 2.9; 30 and 6.7% (P<0.001) increase index of EIDV 38.8% (P<0.001). Resistive and pulsatility indices declined by 5.9 and 9% (P<0.001). After treatment EDV rate was higher than the initial by 13.6% and the shear stress at rest and after the stimulus increase to 10.9 and 5.8% (P<0.001). BA sensitivity to shear stress significantly increased by 60% (P<0.05).

The analysis of the data showed that the treatment of patients with FC I chronic heart failure with beta blockers

has reduced the level of vWF from baseline by 4.1 and 7.7%, respectively, in groups 1 and 2 (P<0.001). When class II CHF decline was 15.3 and 21.4% from baseline (P<0.001), while FC III heart failure - in the first group had a tendency to decrease and patients of the second group was 23.3% reduction (P <0.001) from baseline.

When studying correlations between endothelium-dependent vasodilation and VWF levels in patients before treatment, we found a negative correlation dependence: in group 1 − r=-0,325; in group 2 − r=-0,385 (P<0,01). In our opinion, this may indicate a rise in the relative content of VWF in plasma in patients with CHF in violation of endothelial vasomotor function.

Studying the correlation between the endothelium-dependent vasodilation and the level of von Willebrand factor in patients before treatment, we found a negative correlation dependence: in group 1 - r=-0,325; in group 2 - r=- 0,385 (P<0.01). In our opinion, this could indicate an increase of the relative content of vWF in plasma in patients with CHF in violation of endothelial vasomotor function.

After 6 months of therapy, a close negative correlation between these in-dicators remained in both groups. VWF level depends on the degree of functional class, the largest of its magnitude was observed in patients with FC III. Changes of vWF level reflect endothelial functional state in patients with CHF. Reduction of von Willebrand factor, mostly in patients of group 1, reflects a corrective effect of therapy on endothelial state and severity of dysfunction.

4. Conclusions

In patients of CHF the process of left ventricular remodeling associated with vascular remodeling caused by endothelial dysfunction. Endothelial dysfunction in patients with CHF is associated with the progression of the disease and is characterized by decreased of EDV, severe paradoxical vasoconstriction, significant reduction in velocity parameters, increased secretion of humoral markers of endothelial dysfunction - von Willebrand factor. Thus, during prolonged treatment of patients with CHF FC I-II with the inclusion of β-blockers - bisoprolol and carvedilol improves endothelial function, there was an increase EDV, diameter and blood flow velocity, lowering the tone of blood vessels and increase the sensitivity of the BA to shear stress. In patients with CHF FC III carvedilol is more pronounced than bsoprolol improves endothelial dysfunction.

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