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The Efficacy of Omega-3 Polyunsaturated Fatty Acids on Indicators of Endothelial Dysfunction in Chronic Heart Failure

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Abstract The study included 103 male patients aged from 40 to 55 years with postinfarction myocardial fibrosis. The patients were divided into three groups of functional class (FC) of CHF according to the New York Heart Classification (NYHA) according to the test of 6-minute walk (TSMW): 1 group consisted of 28 patients with CHF FC I; 2 - 46 patients with FC II; 3 - 29 patients with FC III classification NYHA. The control group consisted of 20 healthy volunteers. 62 patients - 15 (I FC), 28 (FC II) and 17 (III FC) received omega-3 polyunsaturated fatty acids at a dose of 1 g per day. The efficacy was evaluated after 6 months. Use of omega-3 polyunsaturated fatty acids CHF patients improves endothelium-dependent vasodilation and. It reduces the activation of oxidative stress, characterized by a decrease in the level of MDA, AGP and $ONOO^-$, increased activity of antioxidant enzymes.

Keywords Chronic heart failure, Endothelial dysfunction, Omega - 3 fatty acids

1. Introduction

Chronic heart failure (CHF) is not only a medical but also a social problem due to the high prevalence, high mortality rates and the high cost of treatment of patients. Myocardial infarction (MI) is one of the causes of heart failure: postinfarction remodeling of the left ventricle (LV) is accompanied by structural and functional changes and impaired systolic and diastolic function. In the early stages of LV dysfunction is an activation of neurohumoral systems: increased activity of the sympathetic-adrenal system (SAS) promotes activation of the renin-angiotensin-aldosterone system (RAAS), and other neurohormones and mediators, including cytokines, endothelin system natriuretic peptide [1] in patients with chronic heart failure remodeling processes affect not only the chambers of the heart, and peripheral vascular endothelial dysfunction that conditionality [3, 4]. Essentially, the development of latest violation is a bioavailability of endothelium product nitrogen oxide II (NO). Therefore, inhibition of NO synthesis is considered as one of the major pathogenetic mechanisms of progression of chronic heart failure (CHF) [2,6,7]. The associated depletion of the body's antioxidative system develops the disorder, called an oxidative stress (OS). It was the evidence for a role on the pathogenesis of CHF OS as well as ischemic and non-ischemic etiology. Reactive oxygen species produced during amplification oxidative stress can damage the vascular endothelium and to reduce the secretion of nitric oxide (NO). This leads to a worsening of endothelial dysfunction, manifested enhanced vasoconstriction, hypercoagulable and proliferation of smooth muscle cells [8]. It is proved that the main markers of endothelial dysfunction is to reduce endothelium-dependent vasodilation vessels, changes in the blood levels of regulatory peptides: endothelin-1, von Willebrand factor [10]. The leading role in the development of OS belongs to a breach of the bioavailability of endothelium-produced nitric oxide (NO). This concept is confirmed by various experimental and clinical studies. Reduced levels of antioxidants can enhance the accumulation of reactive oxygen species in CHF. High serum levels of the markers correlate with OS myocardial dysfunction, severity of the condition and well-known poor prognostic markers, such as the deterioration of functional class, an increase in C-reactive protein, brain natriuretic peptide. Thereupon, particular interest is the investigation of using omega-3 polyunsaturated fatty acids for patients who are suffered with CHF. The study GISSI-Prevenzione involved 11,324 patients with myocardial infarction. The efficiency of standardized capsules of omega-3 PUFAs. It was found that after 3.5 years of mortality decreased significantly in patients treated with omega-3 PUFA. As

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shown by the following analysis, the reduction of mortality in this group of patients is due to a decrease in the frequency of sudden death [1, 3, 4]. There is evidence that omega-3 fatty acids affect the metabolism and energy in the myocardium remodeling through the impact on the system of PPAR-retseptorov. Through the investigation of GISS-HF there were included almost 7000 patients were gotten Heart Failure . Using of the Omacor in a dose of 1gr per a day for an average of 3.9 years, which is caused a significant decrease at the risk of death by any cause 9% was compared with placebo. Currently, the modern guidelines for the treatment of CHF are three types of drugs: basic, additional and supplementary. The main drugs are a group of drugs, the effect of which was proved. These include ACE inhibitors / angiotensin receptor antagonists II, β-blockers, aldosterone receptor antagonists, diuretics, cardiac glycosides and ethyl esters of polyunsaturated fatty acids (eicosapentaenoic and dokozogeksaenoic). The aim of the research - to study the effectiveness of omega-3 polyunsaturated fatty acids on endothelial function and oxidative stress in patients with chronic heart failure.

2. Materials and Methods of Research

The study included 103 male patients aged from 40 to 55 years (mean age - 53,42 ± 6,2 years) with postinfarction myocardial fibrosis. Prescription myocardial infarction ranged from 2 months up to 3 years and duration of heart failure 2,1 ± 0,5 years. The patients were divided into three groups of functional class (FC) of CHF according to the New York Heart Classification (NYHA) according to the test of 6-minute walk (TSMW): 1 group consisted of 28 patients with CHF FC I; 2 group - 46 patients with FC II; 3 group - 29 patients with FC III classification NYHA. The control group consisted of 20 healthy volunteers. There were observed 62 patients – 15 patients (FC I), 28 patients (FC II) and 17 patients (FC III). Each group was received omega-3 polyunsaturated fatty acids at a dose of 1 g per a day. The study did not include patients with acute cerebrovascular disorder, severe degree of diabetes, heart rhythmical disorder, chronical obstructive pulmonary disease. The efficacy was evaluated after 6 months. Vasomotor endothelial function of the brachial artery (BA) was assessed by Doppler sonography the procedure DS Celemajer (1992) on the unit MEDISONSONOACE-X6 (South Korea) with the use of 70.5 MHz linear transducer. The normal reaction of the brachial artery considered it against the background of the expansion of reactive hyperemia by 10% or more of the original diameter. A lesser degree of vasodilation and vasoconstriction considered pathological reaction. The following parameters were evaluated: D - diameter of the brachial artery, sm; Vs - sictolic blood flow velosity the brachial artery, m/s; Vd - diastolic blood flow velocity in the brachial artery, m/s; Vav - average speed of blood flow in the brachial artery, m/s; Pi - pulsating index: PI = (Vs - Vd)/Vav, relative unit.; Ri - resistive index: Ri = (Vs - Vd)/Vs, relative unit.; EDVD = (D1- D) / Dh100%; K- sensitivity brachial artery, relative unit. From the indicators of lipid peroxidation identifiened malondialdehyde (MDA). On the state of the antioxidant enzyme system was evaluated by enzyme activity superoxide dismutase (SOD) and catalase in blood. Statistical analysis of the results. To evaluate the clinical and laboratory parameters apply modern methods of statistical analysis, integrated in a number of applications - "Statistisa 6.0», Excel for Windows XP. Calculate the mean value (M), an error the average value (m), standard deviation (σ), median (Me), the correlation coefficient gamma (γ), median test was used. Differences were considered significant at $p < 0.05$, which is accepted in biology and medicine.

3. Results

Indicators of endothelial dysfunction, assessed by vasomotor reactions brachial artery revealed that in patients with CHF FC I systolic flow velocity (Vs) to the brachial artery was significantly lower by 19.6% ($P < 0.01$) and diastolic velocity (Vd) 33 4% lower compared with the control group ($P < 0.01$). Background Analysis of the resistance index Ri, reflecting the state of resistance to blood flow distal to the measurements showed that in patients with FC I heart failure the figure was significantly higher than the control group to 9.5%; and pulsatility index, indirectly reflects the tone of the vessel above the control group 13.9% ($P < 0.01$). endothelium-dependent vasodilation (EDVD) in the control group was 11,4 ± 1,7%, and in patients with I FC 22.5% compared with the control group.

Patients with chronic heart failure class II showed a decrease of diameter brachial artery 6.9% compared with the control. Reduction of systolic and diastolic blood flow velocity in brachial artery was 25.9% and 38.2% ($P < 0.01$), respectively, compared with the control group. The average speed of blood flow in patients with FC II of CHF was lower by 29.7%; Resistive and pulsatility indices - above 13.8, and 21.4% compared with those of healthy individuals ($P < 0.01$). There was a decrease of brachial artery endothelium - dependent vasodilation sensitivity to the shear stress in patients with FC II of CHF 31.2 and 26.5% of the control group ($P < 0.01$). The results showed that endothelial dysfunction in patients with chronic heart failure is associated with the progression of the disease and was characterized by a decrease in endothelium-dependent vasodilation expressed the paradoxical vasoconstriction, which were more pronounced in patients with FC III CHF. Reduction of systolic blood flow rate in this group of patients was 26.1%, diastolic - on 57% ($P < 0.001$) respectively compared to the control group. There was a decrease of blood flow velocity and the average of 34.8% compared with those of healthy persons constituting 36,7 ± 1.49 cm / s. In patients with FC III of CHF endothelium-dependent vasodilation was 5 ± 3,9%, respectively, versus 11,4 ± 1,7%, the control group, i.e., this index showed a decrease by 54.7% ($P < 0.001$). It was accompanied by a pronounced

decline in the sensitivity of the brachial artery to the shear stress - 59.7% ($P < 0.001$). Pulsatility and resistive indices were higher than the control group by 35.5 and 28.4% ($P < 0.01$). This endothelium-dependent vasodilation declined in 66% of patients, 28% was observed pathological vasoconstriction, and only 4% of patients endothelium-dependent vasodilation remained normal. Inclusion in the complex therapy of heart failure improved the performance of omega-3 polyunsaturated fatty acids endothelium-dependent vasodilation compared with a group of patients who did not accept it. The most pronounced changes were observed in patients with FC II and III of CHF. In patients with class II heart failure significantly increased endothelium-dependent vasodilation by 10.4% ($P < 0.001$); systolic and diastolic blood flow velocity increased by 2.6% and 11.3%, average speed - by 12.9% ($P < 0.05$) from baseline. Pulsatility and resistive indices declined by 13.4 and 16.7% ($P < 0.05$), which was accompanied by an increase in the sensitivity of the brachial artery to the shear stress by 18.2% ($P < 0.05$). In patients with FC III of CHF systolic, diastolic and mean blood flow velocity increased by 3.4; 24.2 and 6.7% ($P < 0.005$), and resistive and pulsatility index decreased by 9.9 and 10.6% ($P < 0.05$) compared with control group. In pations with FC III of CHF and increased performance endothelium-dependent vasodilation 31.2% ($P < 0.02$), and the sensitivity of the brachial artery to the shear stress - by 28.4% ($P < 0.001$).

And to explore the effect of a six-month treatment of omega-3 polyunsaturated fatty acids on indicators of oxidative stress. The results showed that, given the long-term use of omega-3 polyunsaturated fatty acids in patients with FC I heart failure, a decrease MDA level by 28% ($P < 0,05$), which was accompanied by increase of antioxidant enzymes SOD levels by 30.4% and 29.1% of catalase ($P < 0.05$) as compared to baseline values, respectively, due to the additional antioxidant properties of the drug. Increased antioxidant resources helped reduce the level of $ONOO^-$ at 37,7% ($P <0,001$), which contributed to an increase in eNOS activity and NO metabolites levels at 16,8% ($P < 0,05$).

Reducing the level of $ONOO^-$ was 40,5% ($P < 0,001$). In patients with class III heart failure within six months of observation decrease MDA level was 52,7% ($P < 0,001$). The growth indicators SOD and catalase were 63 and 69% respectively compared to baseline (($P < 0,001$). NO metabolites index increased by 42,3% ($P < 0,05$), which is possible due to a highly significant reduction in the level of $ONOO^-$ by 54% compared with baseline ($P < 0,001$).

4. Disscusion

Thus, in patients with chronic heart failure omega-3 polyunsaturated fatty acids helped to reduce the activation of oxidative stress, characterized by a decrease in the level of MDA, AGP and $ONOO^-$, increase the activity of antioxidant enzymes. Major clinical effects of omega-3 PUFAs are due to the inhibition of arachidonic acid cycle, so that prevent the formation of pro-inflammatory cytokines, increases the formation of anti-inflammatory eicosanoids and inhibition of thrombus formation occurs. Also, due to the influence on the synthesis of nitric oxide, and reduce endothelial dysfunction occurs vasodilatation. Omega-3 fatty acids may reduce the sensitivity of tissues to the action of catecholamines in stress, which contributes to the prevention of myocardial injury stressful [7, 6, 11]. Omega-3 PUFAs have antioxidant effect that is realized by increasing the activity of protective antioxidant systems, in particular of superoxide dismutase, which protects the myocardium from damage during oxidative stress.

The positive effect of omega-3 polyunsaturated fatty acids on indicators of endothelial dysfunction in patients with heart failure may be due to a decrease in vascular resistance, and the weakening of vasoconstrictor responses to angiotensin II, anti-inflammatory and antiplatelet effect of the drug, the results of which were obtained in epidemiological and experimental studies. [2, 5, 12].

5. Conclusions

Use of omega-3 polyunsaturated fatty acids CHF patients improves endothelium-dependent vasodilation and. It reduces the activation of oxidative stress, characterized by a decrease in the level of MDA, AGP and $ONOO^-$, increased activity of antioxidant enzymes.

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