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Endothelial Functions in People with High Normal Blood Pressure Experiencing Regular Exercise

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ABSTRACT

In order to determine the effect of athletics on endothelial function, 75 middle-aged patients with this disorder were examined for 2 years at high normal blood pressure. The first observation group consisted of 37 patients who had normalized diet and daily routine. The second group consisted of 38 patients who additionally experienced regular physical activity in the form of regular runs. The observation period is 90 days. Everyone underwent dopplerography of the brachial artery in a sample with reactive hyperemia on the Sonos-1000 apparatus and biochemically examined the level of nitric oxide metabolite -NO^{2-} in the blood. In patients, a decrease in plasma nitric oxide concentration and accumulation of its metabolite in erythrocytes, a decrease in endothelium-dependent vasodilation, a tendency of vessels to spasm, a vasoconstrictor reaction in a sample with reactive hyperemia were found. Normalization of the diet and day regimen led to an unbalanced activation of the NO system, endothelial hyperstimulation while maintaining its dysfunction. The use of regular jogging in combination with basic recovery provided the normalization of the NO-system and the restoration of the vasoregulatory function of the vascular endothelium, which increased the effectiveness of the treatment.

KEY WORDS: ENDOTHELIAL DYSFUNCTION, HIGH NORMAL BLOOD PRESSURE, DAILY ROUTINE, DIET, EXERCISE.

INTRODUCTION

High normal blood pressure is increasingly found in industrialized countries and is one of the pressing medical and social problems (Medvedev, Gamolina, 2008; Medvedev, Kumova, 2007a). According to modern concepts, it is considered one of the leading pathogenetic factors of chronic heart failure, hypertension, and coronary heart disease, due to impaired endothelial function (Medvedev, Kumova, 2007b; Makhov, Medvedev, 2018a). Endothelium becomes a new target for therapeutic effects in individuals with developing cardiovascular pathology (Zavalishina, 2018a; Mal, Vorobyeva et al., 2018). The influence of the basic treatment of high normal blood pressure on the functional state of the endothelium is being actively studied (Vorobyeva, Medvedev, 2018; Zavalishina, 2018b). The optimization of energy metabolism in the myocardium, using feasible physical activity, the purpose of which is very appropriate for such people, is considered a promising approach to eliminating high normal blood pressure (Mal, Kharitonov,

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2018; Makhov, Medvedev, 2018b). The mechanism of action of muscle loads provides for their positive effect on the state of vascular endothelium through activation of nitric oxide synthesis (Zavalishina, 2018c), which is still poorly understood. The objective of the present study was to determine the effect of physical exertion on vascular endothelial function during treatment of high normal blood pressure.

MATERIAL AND METHOD

75 patients with high normal blood pressure, without concomitant pathology, were examined. The average age of the patients was 34.2±1.2 years. There were 30 men among the examined, 45 women. Depending on the health-improving effect, the patients were divided into two comparable groups: the first was 37 patients whose normalized diet and work and rest; the second - 38 patients, who additionally ran an additional 2 km at a free pace daily. The observation period was 90 days. The control group consisted of 22 healthy individuals, similar in gender and age. All patients underwent echodoplercardiography and dopplerography of the brachial artery in a sample with reactive hyperemia to assess the state of cardiohemodynamics and vasoregulatory function of vascular endothelium using the Sonos-1000 ultrasound complex (Correti, 2002). The level of NO was estimated by the concentration of its stable metabolite, NO^2- in plasma and in red blood cells using a biochemical method (Green, 1982). The results were processed by the method of variation statistics with one-way analysis of variance. The significance of differences was assessed by Student's t-test and Fisher's F-test using Microsoft Excel.

RESULTS AND DISCUSSION

In the examined patients, the systolic function of the left ventricle was preserved: the ejection fraction was 6.14±1.56%. All patients showed signs of vascular endothelial dysfunction: a decrease in the content of nitric oxide in blood plasma by 17.7% and an increase in the accumulation of NO metabolite in red blood cells by 7.8% compared with those in the control group. The examined patients also recorded a decrease in blood flow velocity, shear stress on the endothelium, a positive increase in blood flow velocity with reactive hyperemia, which was negative in healthy patients (Table 1).

The effectiveness of including physical exertion in the patient recovery program in relation to the functional state of the endothelium was determined by analysis of variance. A significant effect of the applied recovery on the shear stress on the endothelium was revealed (Fisher's F-test was 6.57, exceeding the critical level F for this sample (4.67) ($p<0.05$)).

In the first group of patients, against the background of basic improvement, the shear stress on the endothelium increased - by 72.0% in the initial state and by 50% with reactive hyperemia, in the second group, when athletics run included in the rehabilitation scheme, it decreased by 1% in In the initial state and by 6% with reactive hyperemia (Table 2). It is known that the shear stress on the endothelium regulates the transcription of the NO synthetase gene (Glagoleva, Medvedev, 2018; Oshurkova, Medvedev, 2018a).

Table 1. Indicators of the functional state of vascular endothelium in the examined

Index	Sick, n=75	Almost healthy, n=22
Vo, m/s	0.66±0.09*	0.77±0.05
D_o,x10^{-2}, m	0.43±0.06*	0.37±0.04
τ_o, x10^{-6} dean x m^2	530.4±5.65	548.4±3.84
V_1, M/C	0.66±0.07	0.75±0.10
D_1 , x 10^{-2}, m	0.44±0.04*	0.42±0.05
τ_1, 10-6 dean x m^2	573.6±6.9	596.2±7.23
NO2- in plasma, nmol/ml	104.5±3.18*	123.0±4.17
NO2- in red blood cells, nmol/ml	80.1±1.20	74.3±0.99

Note: V– is the blood flow velocity in the brachial artery, D – is the diameter of the brachial artery, τ – is the shear stress on the endothelium, index 0 – is at rest, index 1 – is for reactive hyperemia; the significance of differences is *p<0.05, n is the number of subjects. In the following table, the notation is similar.

The concentration of NO^2- in the blood plasma of patients of the first group during therapy was increased to a greater extent (by 8.8%) than in patients of the second group (by 4.2%). The concentration of NO^2- in erythrocytes against the background of basic recovery increased in the first group (by 8.9%) and decreased in the second with additional prescribing runs (by 14.0%), which indicated the activation of NO metabolism. The dynamics of NO^2-concentrations in plasma and erythrocytes against the background of basic recovery can be regarded as an unbalanced activation of the NO-system while maintaining its dysfunction (Zavalishina, 2018d; Makhov, Medvedev, 2018c), and when jogging is included in the recovery scheme, as a balanced normalization of the NO-system.

By the end of the observation period, the vascular tendency to spasm remained in the first group of patients, manifested by an increase in blood flow velocity against the background of an increase in the diameter of the brachial artery by 19.6% at rest and by 26.4% with reactive hyperemia. This reflects the presence of hyperstimulation of the endothelium while maintaining its dysfunction 90 days after the start of recovery with basic drugs. In the second group of patients, the dynamics of observation recorded a decrease in blood flow velocity against the background of an increase in the diameter of the brachial artery by 1.6% at rest and by 4.7% with reactive hyperemia, which indicated an improvement

in vascular endothelial function during regular runs (Zavalishina, 2018e; Vatnikov, 2019).

Patients experiencing regular muscle loadings noted a decrease in the number of cases of destabilization of blood pressure, headaches, increased physical performance in a shorter time compared with patients who received only basic recovery. The inclusion of regular physical activity in the rehabilitation scheme, according to the results of analysis of variance, increased the effectiveness of treatment (Fisher's F-test was 12.86, exceeding the critical level F for this sample (3.98) ($p < 0.001$)).

The positive effect of physical activity on the vascular endothelium is due to their weakening of the activity of systolic influences and the activation of acetylcholine receptors (Makhov, Medvedev, 2018d; Zavalishina, 2018f), which causes an increase in the synthesis of NO (Oshurkova, Medvedev, 2018b). An important feature of physical activity is their ability to stimulate the production of the physiologically necessary amount of NO, which exerts a normalizing effect on vascular tone (Zavalishina, 2018g; Zavalishina, 2018h).

The synthesis of NO with the participation of NO-synthase mainly comes from the amino acid L-arginine, and as suggested from L-citrulline, since it can increase the level of L-arginine. L-arginine is a part of proteins and is present in ordinary protein foods. A lot of this amino acid in seafood, nuts, seeds, seaweed, rice and soy. In addition, L-arginine can be synthesized in the body from citrulline, for example, in the kidneys. It is also synthesized in the liver, although it is completely reutilized in the urea cycle. The content of L-arginine in plasma depends on age and metabolism, and mainly depends on catabolism-the intake of this amino acid in the body. Extracellular L-arginine is rapidly absorbed by vascular endothelial cells and, in the presence of molecular oxygen and NADP, is rapidly oxidized to NO.

Table 2. Endothelial activity on the background of health effects

Index	First group of patients, n=37		Second group of patients, n=38	
	Before treatment	after treatment	Before treatment	after treatment
V_o, m/s	0.63±0.07	0.70±0.06**	0.68±0.08	0.74±0.06
D_o, x 10^{-2}, m	0.45±0.08	0.44±0.05	0.42±0.09	0.40±0.04
τ_o, x10^{-6} dean x m^2	527.0±4.86	534.7±6.12**	539.6±3.46	541.5±4.27*
V_1, M/C	0.63±0.05	0.69±0.04	0.69±0.03	0.73±0.08*
D_1, x 10^{-2}, m	0.42±0.04	0.40±0.02*	0.46±0.06	0.41±0.05
$\tau 1$, 10^{-6} dean x m^2	570.5±5.60	577.6±4.72**	578.9±6.03	589.7±3.20*
NO^{2-} in plasma, nmol/ml	102.4±4.10	114.5±2.23	106.3±2.75	120.3±1.83
NO^{2-} in red blood cells, nmol/ml	83.2±1.34	79.6±0.94	77.6±0.86	75.6±0.63*

This is a whole chain of events that is catalyzed by the enzyme NO-synthase, which has an arginine binding site. There are several forms of NO-synthase - neuronal, inducible and endothelial. Endothelial and inducible NO-synthases are constitutional and are controlled by intracellular calcium and calmodulin. Neuronal NO-synthase requires gene transcription, is calcium independent and is expressed during muscle activity during development, as well as by macrophages and other tissues in response to inflammatory mediators. In addition, L-arginine is involved in other metabolic processes unrelated to NO-synthase, for example, in the urea cycle, and it also has a strong Sokogonny effect.

Infusion of arginine at rest increases the level of insulin, glucagon, growth factor, prolactin and catecholamines. Such hormonal changes affect metabolism, in particular glucose and fat levels. It is assumed that the growth factor influences exercise performance, increasing fat oxidation and saving glycogen stores, as well as stimulating the release of an insulin-like growth factor, contributes to the absorption of amino acids and protein synthesis. It also improves exercise through increased muscle mass and strength. Arginine affects some indicators of physical performance in untrained and low-trained people. The decrease in metabolic products (ammonium, potassium) observed in some articles is associated with an increase in dilution of these products due to an increase in blood flow due to the synthesis of NO. However, there is no evidence of the effect of high doses of arginine consumed with food on blood flow in healthy people.

Studies on well-trained athletes have shown that a combination of arginine with aspartate can cause biochemical changes in the blood, which is not always confirmed by other researchers, but nevertheless a general conclusion is made - these additives do not significantly affect exercise. The lack of a pronounced effect in trained athletes is associated with physiological and metabolic adaptations due to regular physical activity. The fact of the effect of exercises on endothelial function is well established - regular exercises during the week increase the activity of endothelial nitric oxide. It is likely that activation of endothelial function is a systemic rather

than a local reaction, with significant muscle load. And probably the activation of the pulmonary, cardiovascular and nervous systems due to regular training significantly exceeds the possibility of activation caused by taking arginine with food. However, there are other factors that can reduce the effectiveness of arginine - this is the ratio of arginine/lysine. Lysine competes with arginine for entry into the cell (intracellular active transport) and inhibits arginase; under normal conditions, the food ratio of arginine / lysine should not exceed 2.5.

CONCLUSION

Persons with high normal blood pressure are characterized by signs of vascular endothelial dysfunction: a decrease in the concentration of nitric oxide in blood plasma and the accumulation of its metabolite in red blood cells, a decrease in endothelium-dependent vasodilation and a tendency of vessels to spasm. Improvement of these individuals through normalization of the diet and the regime of work and rest leads to an unbalanced activation of the NO system, hyper-stimulation of the endothelium while maintaining its dysfunction. An additional purpose of physical activity leads to the normalization of the NO-system and the restoration of the vaso regulatory function of vascular endothelium, increasing the effectiveness of the treatment of high normal blood pressure.

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