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Influence of L-arginine (Tivortin®) on imbalance of essential amino acids of blood plasma in patients with stable angina pectoris

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Abstract
Patients with stable angina (SA) were examined with application method of ion-exchange liquid-column chromatography. In the blood plasma the content of essential amino acids (EAAs) was determined: arginine, valine, histidine,isoleucine, leucine, lysine, methionine, threonine, tryptophan, phenylalanine. The patients are divided into two groups: I group - 33 persons who received cardcet, bisoprolol, atoris, enap, acetylsalicylic acid, clopidogrel; II - 35 people, the therapy of which, in addition to the named drugs, included 10 infusions by100 ml of L-Arginine (Tivortin®), Yuria-Farm). The control group included 20clinically healthy individuals. The results of the study indicate a different dynamics of changes in the level of EAAs in blood plasma in patients with SA who received antianginal therapy and antianginal therapy with L-arginine. It should be noted that in patients with Group I after treatment, the level of EAAs has significantly decreased, and in patients of the II group - has significantly increased comparatively with values before treatment. In patients with SA who received baseline therapy and L-arginine, in contrast to patients receiving baseline therapy, in blood plasma normalizes the level of arginine that promotes the synthesis of NO; the level of amino acids (AA) with branched side chain normalized (valine, leucine and isoleucine), which provide synthesis of large quantities necessary compounds (peptides, sterol, ketone bodies, glucose); a normal level of lysine was maintained, which contributes to adequate flow metabolic transformations of this AA. Against the background of receiving baseline therapy and L-arginine in patients with SA compensatory replenishment and intravascular retention were noted level of histidine with its enhanced intracellular metabolism. Thus, the use of L-arginine in a complex treatment patients with SA corrects an unbalanced AA of plasma, and therefore, favorable affects the improvement of physiological processes in conditions of myocardial ischemia.

Keywords: stable angina pectoris, essential amino acid, L-arginine, baseline therapy

Introduction
Many risk factors for coronary heart disease (CHD) have been shown to reduce the synthesis and / or bioavailability of the endothelium. Nowadays. a new therapeutic concept for the treatment of patients with coronary heart disease is being developed. whose purpose is to restore adequate bioavailability of NO and. as a result. to improve endothelial-dependent vasodilation. In this aspect. one of the most promising directions is the use of the natural precursor NO-L-arginine [4, 5, 8, 12].
The average daily intake of L-arginine (Tivortin®) is 5.4 mg. The physiological need of tissue organs of most mammals in arginine is satisfied with its endogenous synthesis and / or food intake.
Convincing experience of effective use of L-Arginine in the treatment of cardiovascular diseases (CVD) has been obtained.
In patients with stable angina (SA). L-arginine causes a decrease in dysfunction of the brachial artery endothelium. improves tolerance to physical activity (a significant increase in the time of pedaling and the amount of work performed). The use of L-arginine contributed to improving the quality of life of patients (significantly reduced the consumption of nitroglycerin). many patients stopped resting. Treatment did not lead to significant changes in blood pressure. heart rate. did not cause clinically significant changes in laboratory parameters. lipid and carbohydrate profiles [1, 2, 3] did not change. On the background of treatment with L-arginine. a statistically significant decrease in the aggregation of amino acid-induced platelet aggregation has been established. which makes its effect similar to that of acetylsalicylic acid. Given the role of L-arginine in the inflammation cascade. it can be assumed that the drug reduces platelet sensitivity to inflammatory mediators. The results of the evaluation of plasma hemostasis showed a significant decrease in the fibrinogen level. indicating a decrease in coagulant potential. blood coaguloblacity. Thus. the results of numerical studies of recent years. which we tried to generalize in this paper. indicate the possibility of effective and safe use of the properties of L-arginine as an active donor NO in clinical practice with a variety of pathologies. It was advisable to study the effect of L-arginine on the amino acid spectrum (AAS) of blood plasma in patients with SA.

Material and methods of research
67 patients with SA at the age from 58 to 75 years old (mean age - 67.2 years ± 5.2 years) were examined. and they were divided into two groups: I group - 33 patients received bisoprolol 5 mg. enalapril 10 mg. atorvastatin 20 mg. acetylsalicylic acid 75 mg. isosorbide dinitrate 20 mg. group II - 35 patients received bisoprolol 5 mg daily. enalapril 5 mg twice daily. atorvastatin 10 mg per day. acetylsalicylic acid 75 mg daily. isosorbide dinitrate 10 mg twice daily day and L-arginine 4.2 g - 10 infusions (Tivortin®). Yuriy-Farm). The examination of patients was carried out at the beginning of the appointment of treatment and after 20 days. The control group (CG) included 20 clinically healthy people aged 50-60 years (average age - 55.6 years ± 4.8 years).
AAS blood plasma was studied by ion exchange liquid-column chromatography. Identified essential amino acids (EAA): arginine. valine. histidine. isoleucine. leucine. lysine. methionine. threonine. tryptophan. phenylalanine.

Results of the research and their discussion
Data on different dynamics of changes in the content of amino acids (AA) in blood plasma in patients with SA depending on the treatment were obtained. The total amount of blood plasma

in the patients of both groups after treatment remained significantly lower than that of the CG. However. in patients receiving L-arginine (Tivortin®). the overall level of AA significantly increased compared with the indicator before treatment at 61.5 μmol100 ml (P <0.05). which may indicate an increase in the anabolism of AA.

It should be noted that patients with Group I after treatment significantly decreased EAA levels by 34.8 μmol / 100 ml (P <0.01) compared with values prior to treatment. In patients with Group II. at the end of the observation. EAA in blood plasma significantly increased in comparison with those before treatment at 45.0 μmol / 100 ml (P <0.05) and 20.3 μmol / 100 ml (P <0.05) (Table 2). 1

Table 1: Influence of bass therapy on the spectrum of plasma NSAIDs in patients with stable angina pectoris. μmol / 100 ml (M ± m)

Indicator	CG(n = 20)	Before treatment (n = 33)	On the background of treatment (n = 33)
Lysine	21.98 ± 1.50	21.51 ± 1.9	22.78 ± 1.20
Hystidine	10.51 ± 1.28	8.86 ± 0.10*	6.89 ± 0.05*#
Arginine	8.34 ± 0.35	6.75 ± 0.50*	9.25 ± 0.06#
Thoronine	17.4 ± 1.37	9.85 ± 1.35*	13.846 ± 1.05*#
Valin	29.03 ± 2.42	14.4 ± 0.7*	24.44 ± 1.30*#
Methionine	3.43 ± 0.07	3.61 ± 0.07	2.098 ± 0.05*#
Isoleucine	7.25 ± 0.42	5.32 ± 0.05*	7.96 ± 0.08*
Leucine	14.34 ± 1.26	9.57 ± 0.09*	13.77 ± 0.60*
Fenilalanine	8.46 ± 0.35	6.58 ± 0.09	5.7 4 ± 0.09*

Notes: * - a significant difference with respect to the control group; # Is a significant difference in treatment.

Patients with SS who received baseline therapy determined a significant reduction in the level of arginine of 5.3 μmol / 100 ml (P <0.05). which may indicate the activation of the intracellular metabolism of this AA. as well as enhanced synthesis of its derivatives. in particular. the synthesis of NO. which affects the aggregation and adhesion ability of the platelets. reducing the ability to thrombogenesis and reducing the vascular reactivity of atherosclerotic changes in the arteries and contributes to the formation of collagen in the walls of the vessels. In patients treated with L-arginine. these levels of AA significantly increased compared with the rate before treatment at 2.5 μmol / 100 ml (P <0.05) and normalized (Table 2).

Thus. the additional ingestion of arginine in the human body can maintain its level in the blood plasma. and. therefore. create conditions for the synthesis of NO. an important compound that has anti-atherogenic properties.

Table 2: The effect of basic therapy. which included L-arginine (Tivortin®). on the amino acid plasma spectrum of blood in patients with stable angina pectoris. μmol / 100 ml (M±m)

Indicator	CG(n = 20)	Before treatment (n = 34)	On the background of treatment (n = 34)
Lysine	21.98 ± 1.50	21.51 ± 1.90	14.28 ± 1.00*#
Hystidine	10.51 ± 1.28	8.66 ± 0.20*	4.61 ± 0.09*#
Arginine	8.34 ± 0.35	6.49 ± 0.09*	1.19 ± 0.06*#
Thoronine	17.40 ± 1.37	9.64 ± 1.46*	5.97 ± 0.45*#
Valin	29.03 ± 2.42	14.58 ± 0.4*	10.0 ± 0.06*#
Methionine	3.43 ± 0.07	2.61 ± 0.05	1.64 ± 0.02*#
Isoleucine	7.25 ± 0.42	4.64 ± 0.04*	2.38 ± 0.06*#
Leucine	14.34 ± 1.26	9.06 ± 0.08*	6.25 ± 0.08*#
Fenilalanine	8.46 ± 0.35	6.79 ± 0.07*	5.7 0± 0.07*

Notes: * - a significant difference with respect to the control group; # Is a significant difference in treatment.

In patients with SA under the action of basic therapy in blood plasma. a significant reduction in lysine content was detected - by 7.23 μmol / 100 ml (P <0.01). In patients with SA who received antianginal therapy and L-arginine (Tivortin®). the level of lysine did not significantly change. Lysine forms a bond between transaminases and pyridoxal phosphate. since it has two amino groups in its composition: one affects the peptide bond with transaminase proteins. the second retains the reserves and the integrity of pyridoxalphosphate. Lysine participates in the formation of collagen. strengthening the vascular wall. in the formation of carnitine. promotes the utilization of FA for the energy potential of cells and the preservation of immune reactivity of the body [7]. Consequently. with such therapy. a sufficient (normal level) of this AA in the blood plasma is maintained. which ensures the normal course of the above reactions.

Patients with SA had a significant decrease in valine levels at 4.59 μmol / 100 ml (P <0.01). isoleucine was 2.26 μmol / 100 ml (P <0.05) and leucine at 2. 8 μmol / 100 ml (P <0.05). In patients with SS who received L-arginine (Tivortin®) therapy. valine levels increased significantly by 10.1 μmol / 100 ml (P <0.05). isoleucine - by 2.64 μmol / 100 ml (P <0.05) and normalized. the level of leucine was 4.2 μmol / 100 ml (P <0.05) and normalized.

Valine. leucine and isoleucine - EAA with branched side chain - Branched chain amino acids (BCAA). protein [10]. In the first stage of catabolism. one and the same enzyme catalyzes the transamination of all three AKs to form corresponding branched α-ketoacids. which subsequently undergo oxidative decarboxylation. resulting in acyl-CoA and succinyl-CoA. For BSAA is characterized by a general strengthening effect on the heart. which is proved both in animals and in humans [11]. It has been established that BCAA promotes mitochondrial biogenesis in the myocardium and other muscles. preventing oxidative stress. increasing physical endurance. thus prolonging life (in an experiment in rats) [13].

Thus. decreasing levels of valine. isoleucine and leucine may indirectly indicate an increase in the synthesis of acyl-CoA and succinyl-CoA compounds that enter the Krebs cycle. Consequently. with myocardial ischemia. the catabolism of valine. leucine and isoleucine increases. and the addition to antianginal therapy L-arginine (Tivortin®). provides depot of these AA.

In patients with SA. under the action of basic therapy. a significant decrease in histidine was observed at 4.05 μmol / 100 ml (P <0.05). and in patients receiving baseline and L-arginine (Tivortin®). the level of this AA significantly decreased by only 1. 97 μmol / 100 ml (P <0.01). In addition. a significant difference was found in the level of this AK in patients with I and II groups at the end of treatment at 2.28 μmol / 100 ml (P <0.05). Histidine has a vasodilator effect. normalizes the lipid composition of blood. is one of the most important regulators of blood clotting [6]. With histidine. histamine is formed. which. along with other actions. helps lower blood pressure. dilates blood vessels.

Reducing the level of histidine in blood plasma in patients with SA after treatment may indirectly indicate an improvement in the function of glycoprotein and C-protein. an important regulator of blood clotting. and. consequently. a reduction in the risk of thrombotic formation. Thus. in patients with a stable course of CHD there is an increased cholesterol catabolism of histidine. Treatment. which includes L-arginine (Tivortin®). to some extent compensates for the costs of this AA.

Patients with SA under the action of basic therapy showed a significant decrease in the level of threonine in the blood plasma - 3.67 μmol / 100 ml (P <0.05). In patients with II. the level of this AA significantly increased compared with the rate before treatment at 3.21 μmol / 100 ml (P <0.05). although it remained significantly lower than that of 3.56 μmol / 100 ml (P <0. 05). Threonin improves the state of the cardiovascular system. the liver. This AA also participates in the synthesis of glycine and serine. which strengthen the ligaments and all muscles. including myocardium [7]. Along with methionine is

involved in the decomposition of fats and fatty acids [9]. Reducing threonine levels in patients with SA after antianginal therapy may indicate a decrease in energy levels and increased use of it for the synthesis of glycine and serine. Consequently. the addition of L-arginine (Tivortin®) to treatment of patients with SS promotes compensatory increase in the level of threonine.

Analyzing the results of the study. it is evident that in patients with I and II groups there are unidirectional changes in the level of methionine in blood plasma after treatment. The level of this AA significantly decreased after treatment by 0.97 μmol / 100 ml (P <0.05) and 1.5 μmol / 100 ml (P <0.05). respectively. In addition. the rates in both groups after treatment were not significantly different.

In patients with SA who received baseline therapy. and baseline therapy with L-arginine (Tivortin®). no significant differences were found regarding the level of phenylalanine in blood plasma.

It should be noted that in patients with SA in both groups after treatment. there was a significant decrease in the level of ammonia in plasma - 6.37 μmol / 100 ml (P <0.05) and 24.75 μmol / 100 ml (P <0. 01). In patients receiving baseline therapy and L-arginine (Tivortin®). the level of ammonia in the blood plasma normalized.

Thus. the use of L-arginine (Tivortin®) in the complex treatment of patients with SA corrects the plasma AA imbalance. and therefore. has a beneficial effect on the improvement of physiological processes and conditions of myocardial ischemia.

Conclusions

1. In patients with SA who received baseline therapy and L-arginine (Tivortin®). the blood plasma significantly increased the overall level of AA and EAA. which indicates the predominance of anabolism processes over the processes of catabolism with MI.
2. In patients with SA who received basic therapy with L-arginine (Tivortin®). in the blood plasma significantly increased the level of AA with branched side chain. which. due to the peculiarities of its structure. perform important functions in the body: the synthesis of peptides. sterol. ketone bodies. glucose.
3. In patients with SA who received baseline therapy and L-arginine (Tivortin®). in contrast to patients receiving only baseline therapy. the blood plasma normalized the level of arginine. which probably contributes to the synthesis of NO.
4. Against the background of receiving basal therapy and L-arginine (Tivortin®) in patients with SA. in contrast to patients receiving baseline therapy. the level of lysine in the blood plasma was maintained at normal levels. which contributed to the adequate flow of metabolic transformations of this AK.
5. In patients with SA who received baseline therapy and L-arginine (Tivortin®). in contrast to patients receiving only baseline therapy. the level of valine. leucine and isoleucine was normalized in the blood plasma. which ensure the synthesis of a large number of required compounds.
6. Against the background of basal therapy and L-arginine (Tivortin®) in patients with SA. compensatory replenishment and maintenance of the internal vascular level of histidine with increased intracellular metabolism was noted. as evidenced by a significant decrease in this level of AA in patients with SA who received antianginal therapy only.
7. Against the background of basic therapy and L-arginine (Tivortin®) in patients with SA. a significant increase in the level of threonine was found. which provides the normal metabolism of this AA with enhanced intracellular.
8. In patients with SA on background therapy. the level of ammonia in blood plasma was significantly lower than that of treatment. and in patients who. in addition to anti-anginal therapy. L-arginine (Tivortin®) was prescribed. the level of ammonia in blood plasma was normalized.

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