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Influence of antianginal therapy and L-arginine on spectrum of non-essential amino-acids in blood serum of patients with unstable angina

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Abstract
The study involved 67 patients with unstable angina, aged from 59 to 74 years (average age of patients was 67.2 ± 5.2 years) and 18 healthy subjects between the ages of 50 to 65 years (average age was 56.2 ± 4.7 years). Object of study was amino acid (AA) of blood serum. We used the method of liquid-ion exchange column chromatography. The blood plasma was determined following AA: alanine, aspartic acid, glycine, glutamine, glutamic acid, ornithine, proline, serine, taurine, tyrosine, cysteine. We investigate patients before and after treatment (after 15-17 days). All patients received conventional antianginal therapy as following; beta-blocker (konkor or Bisoprolol - 5 mg), antiplatelet agents (Acetylsalicylic acid - 75 mg), statins (Atorvastatin 10 mg), ACE inhibitor (Enalapril 10 mg). In addition to these medicinal drugs patients were assigned intravenously 100 ml L -arginine (Tivortin) once a day. A total of 6 infusions. Patients with Unstable Angina compared with the control group (CG) showed a significant decrease in the vast majority of non-essential AA (glutamic acid, proline, serine, taurine, cysteine), which indicates an increase in its catabolism.
In patients under the influence of antianginal therapy with L-arginine occurs a significant decrease of following serum AA: alanine, aspartic acid, glycine, glutamine, serine and tyrosine, which is probably due to the increased use of the AA for the synthesis of biologically active substances that generally possess protective features. Under the influence of therapy significantly increases the content of ornithine, which can be seen as a defensive response, as ornithine, participates in the ammonia neutralization cycle. On the background of treatment in patients with Unstable Angina significantly increases the content of taurine, which probably will facilitate the entering of the AA to the myocardium as a cardioprotector. Antianginal therapy including L-arginine resulted in a significant increase in the serum content of cysteine as a substrate for the synthesis of hydrogen sulfide (H_2S), which can be considered as a compensatory response to myocardial ischemia.

Keywords: Unstable angina, amino acid, antianginal therapy, L-arginine.

1. Introduction
Formulation of problem. Cardiovascular diseases (CVD) are the leading cause of death and disability of the population in most countries. It is expected that by 2030 more than 23 million patients have died from these diseases and they will take first place among the causes of death of the world's population. However, if in the developed countries, the number of deaths from cardiovascular disease is reduced, in other countries it is quickly increasing. Ukraine is among the last one. Among the CVD in adults leads hypertension, coronary heart disease (CHD) and 3 times [8].
Among CVD acute myocardial infarction (MI) is the most that associated with a significant contagion among people of working age and its high mortality rate. Every year in Ukraine registered about 50,000 cases of MI [19]. This statistics of deaths from this disease remains high - from MI die 5% of the population [9, 18]. High attention is paid to the unstable angina, which in 25-35% of cases is preceded by the development of myocardial infarction [21].
Despite significant advances in management of patients with unstable angina, clinicians and researchers are constantly working to optimize the treatment of this disease.
This is no doubt in the importance of pathogenic significance of violations of protein metabolism in patients with coronary artery disease. It is known that metabolic products of AA are biogenic amines, which operate multifaceted role in biochemical processes. However, information about the state of the spectrum free AA in blood of patients with ischemic heart disease are sporadic. There were analyzed only some AA [15, 23]

Nowadays, it is developing a new therapeutic treatment for patients with coronary heart disease, the aim of which is to restore adequate bioavailability of nitric oxide (NO) and as a result – improvement of endothelium-dependent vasodilation. In this aspect, one of the most promising way is the use of natural precursor of NO - L-arginine. There are already some investigations which testifying to the effectiveness of L-arginine (Tivortin) in patients with stable angina II-III functional class [13, 16, 17, 11].

Tivortin is an artificially prepared arginine, which is a structural material for endothelial NO synthase which catalyzes the synthesis in endothelial NO (reduced activation and adhesion of leukocytes and platelets), and suppresses the adhesion of protein synthesis, which prevents the occurrence both of cardiovascular events as pancreatitis ischemia (or pancreatic infarction in these patients). NO improve endothelium-dependent dilation [10], which was the basis for FDA (Food and Drug Administration) to recommend the use of L-arginine in the treatment of refractory angina, coronary heart disease and congestive heart failure [6].

There were no investigations to find out the effect of drug treatment on a range of blood AA-free content in patients with CHD.

2. Objective: To study the effect of anti-anginal therapy, including L-arginine on the spectrum of non-essential amino acids in patients with unstable angina.

3. Material and Methods: The study involved 67 patients with unstable angina aged from 59 to 74 years (average age of patients was 67.2 ± 5.2 years), 18 healthy subjects between the ages of 50 to 65 years (average age was 56.2 ± 4.7 years). The diagnosis of the unstable angina established by order of the Ministry of Health of Ukraine from 03.07.2006 ie. № 436 "Protocols of medical care in the specialty "Cardiology ". The survey did not include patients with heart failure II B and III stage, atrial fibrillation, concomitant diseases in the stage of decompensation, cancer, diseases of the musculoskeletal system.

Investigations were carried out before and after treatment (after 15-17 days). All patients received conventional antianginal therapy (beta-blocker (konkor or Bisoprolol - 5 mg), antiplatelet agents (Acetylsalicylic acid - 75 mg), statins (Atorvastatin -10 mg), ACE inhibitor (Enalapril - 10 mg). In addition to these medical preparations patients were assigned intravenous drip injection of 100 ml L-arginine (Tivortin) once a day. A total of 6 injections. The object of investigation was AA in blood serum. We used the method of liquid-ion exchange column chromatography. In the blood serum we studied such non-essential amino acids: ornithine, taurine, aspartic acid, serine, glutamic acid, proline, glycine, alanine, cysteine, tyrosine, glutamine.

The research results were processed on a PC using the software package Microsoft Office. Statistical analysis of the data used by the program Microsoft Excel 2010. The significance of differences between the average performance of different groups provided by determining the Student t-test or Pearson.

4. Results and Discussions: Analyzed the results, it should be noted that patients under the effect of the antianginal therapy with L-arginine showed more significant changes in the vast majority of content of nonessential amino acids. Table 1 shows that in patients with unstable angina content of alanine in serum before treatment were not significantly different from the index of control group, and after therapy it became significantly less compared to control group and to the mark before treatment ($p < 0.01$ in both cases). Alanine is one of the amino acid, which is metabolized till pyruvic acid that enters the Krebs cycle. This amino acid improves immune system by the metabolism of carbohydrates and organic acids, participates in the detoxification of ammonia in the process of gluconeogenesis. It is an intermediate product of metabolism of other AA part of some biologically active compounds, such as nitrogen extractives skeletal muscles - carnosine, anserine, coenzyme, and one of the B vitamins, pantothenic acid. It is part of very important enzyme alanine aminotransferase in the liver, myocardium and other tissues. Alanine aminotransferase is the main indicator of cytolysis. Reducing the level of serum alanine during treatment may indicate enhanced compensatory transformations of alanine as an energy source under conditions of myocardial ischemia [4].

Table 1: Nonessential amino acids in blood serum in patients with unstable angina before and after treatment, Mark / mol / L (M ± m)

NAME OF AA	CG–I	Unstable Ang (Before treatment)- II	Unstable Ang. (After treatment)- III	P I-II	P I-III	P I-II
Alanine	465,3±13,1	460,3±13,3	254,3±6,1	P>0,05	P<0,01	P<0,01
Aspartic acid	21,2±1,1	24,6±1,3	16,23±1,4	P>0,05	P<0,05	P<0,05
Glycine	318,4±22,4	306,5±18,5	220,2±7,3	P>0,05	P<0,01	P<0,01
Glutamine	518,9±24,5	505,9±21,4	285,7±10,5	P>0,05	P<0,01	P<0,01
Glutamic acid	226,4±11,6	119,2±7,5	121,4±6,5	P<0,01	P<0,01	P>0,05
Ornithine	143,6±11,5	157,5±12,4	181,2±13,6	P<0,05	P<0,05	P<0,01
Proline	214,2±12,7	76,6±3,8	78,5±3,5	P<0,01	P<0,01	P>0,05
Serine	187,5±14,3	131,2±6,5	96,2±3,8	P<0,01	P<0,01	P<0,01
Taurine	90,2±4,4	65,5±2,5	84,4±3,5	P<0,05	P<0,05	P<0,05
Tyrosine	63,2±3,8	63,2±2,5	36,6±2,3	P>0,05	P<0,01	P<0,01
Cysteine	68,2±3,1	50,7±1,5	79,5±3,6	P<0,05	P<0,05	P<0,05

Similarly to alanine content in blood serum the level of aspartic acid in the serum of patients with unstable angina before treatment did not differ significantly from the index in control group, and after therapy significantly decreased in comparison with the control group and with the index before treatment ($p < 0.05$ in both cases). Aspartic acid along with other AA is part of different proteins, in the composition of tissues of different organs. Forming an asparagine, aspartic acid plays an important role, linking, transporting and neutralizing ammonia. It takes part in the urea cycle, gluconeogenesis. A significant decrease in the free aspartic acid in the serum of patients with unstable angina under the influence of treatment can be regarded as a strengthening of the intracellular metabolism of AA in terms of myocardial ischemia.

In the patients with unstable angina levels of glycine in the

serum did not significantly differ from the control group (P> 0.05). After treatment there was a significant decrease in the content of AA compared to the control group and with the index before treatment (p <0.01 in both cases).

Porphyrins and purine bases, glutathione, choline, creatine, hippuric acid, conjugates of bile acids, proteins, phospholipids are synthesized with the help of glycine. In the literature there are reports of the antioxidant effect of glycine, which is manifested in reduced lipid content of products of peroxidation - malondialdehyde and diene conjugates [28], and to increase the activity of antioxidant enzymes - superoxide dismutase [32] and catalase. In vitro is proved that the addition of glycine in the complex therapy better regeneration processes occur by reducing the levels of lactic and pyruvic acids. The membrane of myocardial cells are full of receptors which exposure to glycine that may have a cytoprotective effect by inhibiting the flow of calcium ions [32]. Thus it is likely that a significant reduction in the glycine in patients with unstable angina under the influence of treatment may indicate a decrease in lipid peroxidation products, is a defensive reaction in patients with coronary artery disease.

It draws attention to the fact that patients under the effect of the treatment, the content of glutamine is almost reduced twice as compared with CT and with the index before treatment (p <0.01 in both cases). Glutamine is an important component of a variety of metabolic processes. This is the most common free AA. 60% of free AA which are present in the muscle cells are synthesized from glutamine. Glutamine is transporting nitrogen between organs in the body. It proved that glutamine plays a key role in the regulation of synthesis of tripeptide glutathione consisting of glutamate, glycine cysteine. Glutathione protects cells from oxidative damage in the body and is metabolized in practically all tissues. This is an important source of carbon and nitrogen for various substrates. It is an indispensable substrate for the normal functioning of the humoral and cellular immunity. We know about the positive impact of glutathione in patients with impaired vital functions were treated in the ICU [12]. A significant decrease in the level of glutamine in patients under the influence of the unstable angina of the treatment is likely due to the strengthening of its intracellular metabolism, and primarily as cytoprotector.

Patients with unstable angina compared with the CG level of glutamic acid was significantly lower (p <0.01). No significant differences in the level of glutamic acid in the serum of patients with disease after treatment have been identified. Meaning of glutamic acid to the organism: participates in synthesis of histamine, serotonin and other biologically active substances, neutralizes harmful decay product – ammonia, be included in the cycle of transformations of carbohydrates and nucleic acids. [4].

Patients with unstable angina compared with the CG showed significantly higher content of ornithine (p <0.05), and after treatment, this figure has increased significantly more (p <0.05). Ornithine helps to release growth hormone, which helps burn fat in the body. This effect is enhanced when used in combination with ornithine, arginine, and carnitine. Ornithine is also necessary for the immune system and liver function, participating in the process of detoxification and recovery of liver cells. High levels of ornithine are detected in skin and connective tissue, so the AA helps to restore damaged tissue. Ornithine participates in the urea cycle. It can be assumed that this increase in the content of AA in the serum may be indicative of a decrease of its use in the urea cycle. Furthermore possibly decreases its use as a substrate for the synthesis of proline and glutamic acid, as evidenced by the significantly lower content of AA in the serum (both p <0.01). Ornithine is the substrate for the synthesis of arginase - an enzyme that everywhere there are in living organisms, and synthesis of NO [3]. Increased content of ornithine in the blood serum may also indicate a decrease in the synthesis of arginase and synthetase. Under the influence of the treatment showed a significant increase in ornithine blood serum in patients with unstable angina (p <0.01), which may indicate a lack of positive influence on the metabolism of the AA.

Patients with AA compared to CG in the blood serum showed significantly lower content of proline (P <0.01). Proline is the basic biochemical and morphological component of connective tissue. Known as L-proline is responsible for collagen formation. It helps to restore cartilage of joints, strengthens the myocardium. The amino acid sequence in the vicinity of the center of the ATP involves myocardial muscle fibers plot "proline-proline," which dramatically increases the likelihood conformational changes in this area myosin molecules is essential for muscle contraction [14].

Natural AA as lysine and proline form a "Teflon" like layer around the lipoproteins which prevents further deposition of fat in the arterial wall. At the same time, by the same method, the fat molecules are released already formed deposits and are carried through the bloodstream or "bad cholesterol."

This occurs as follows: proline and lysine are able to separate molecules of lipoprotein deposits on arterial walls.

Thus, reducing the content of proline in the blood serum of patients with unstable angina may indicate from one side abuse synthesis reactions proline, ornithine, as evidenced by increased serum ornithine, and on the other side - the increased use of proline for metabolic needs, in particular for the synthesis of collagen. Under the action of antianginal therapy and L-arginine is no significant changes in the level of proline in the blood serum.

Next AA, which drew the attention, was serine. Patients with unstable angina compared with the CG showed significantly lower content of this AA in serum (p <0.01). Serine is a part of the serine proteases are enzymes which, besides its other functions play an important role in the coagulation cascade. Members of this group of proteases, thrombin, trypsin, factors VIIa, IXa, Xa, XIa, XIIa, and protein C. Serine involved in the synthesis of immunoglobulins, pyrimidine, purine, porphyrin creatine. It takes part in deposition of glycogen in the liver, the formation of active centers of many enzymes, among which are esterase - the enzyme which is responsible for the cleavage of esters and ethanolamine - the starting material synthesis of choline.

A significant decrease in the level of serine in patients with Unstable Angina compared to the CG may indirectly indicate enhanced use it for the synthesis of proteases, immunoglobulins and other biologically active substances and the reduction of its synthesis from glycine. After the treatment the content of serine significantly reduced compared to baseline (p <0.01) [4].

In serum of patients with unstable angina compared to the CG there was significantly lower content of taurine (P <0.05). The myocardium is sensitive to deficiency of AA. Of particular importance for the functioning of the myocardium has AA taurine. The share of taurine amino acid composition infarction accounts for about 50%. In the study of the physiological effects of taurine in patients with heart failure were identified his soft cardiotonic and positive inotropic effect. Taurine

relates to replaceable AA, its synthesis depends on the intake of food to and from the amount of methionine in the diet - which is the source of endogenous taurine synthesis. It participates in the synthesis of many other AA, and a part of the main component of bile, which is necessary for fat digestion, absorption of fat-soluble vitamins and to maintain normal levels of cholesterol. Taurine is essential for normal metabolism of sodium, potassium, calcium and magnesium. It prevents the excretion of potassium in heart muscle and therefore affects the prevention of some cardiac arrhythmias. Taurine gives a protection from dehydration of the brain [20].

The therapy in patients with significantly increased content of taurine, which can be interpreted as a positive response ($p < 0.05$). In serum of patients with unstable angina compared to CG level of tyrosine was not significantly different ($p > 0.05$). This vitamin-like substance was first isolated in 1957 from bovine heart mitochondria by the American scientist F. Crane. K. Folkers in 1958 determined its structure. Another official name of Coenzyme Q10 is a ubiquinone (ubiquitous quinone), as it is found in various concentrations in virtually all tissues of animal origin. In the 60 years it was shown the role of Q10 as an electron carrier in the respiratory chain of mitochondria. In 1978 P. Mitchell proposed a scheme for explaining part of coenzyme Q10 in the electron transport in the mitochondria, and in the process of electron transport and oxidative phosphorylation, which was awarded the Nobel Prize [5].

Coenzyme Q10 effectively protects the lipids of biological membranes and lipoprotein particles of blood (phospholipids - "membrane glue") by the destructive processes of peroxidation, DNA and proteins protects the body against oxidative modification by the accumulation of reactive oxygen species. With age biosynthesis of CoenzymeQ10 progressively reduced, and the flow rate at exercise, emotional stress in the pathogenesis of various diseases and increased oxidative stress [2].

More than 20 years of experience in clinical investigations of use of Coenzyme Q10 in thousands of patients convincingly prove role of his deficiency in the pathology of CVD, which is not surprising, since it is in the cells of the heart muscle largest energy needs. The protective role of coenzyme Q10 due to its participation in the processes of energy metabolism and antioxidant properties of cardiomyocytes. The uniqueness of the discussion of the drug - its regenerative capacity under the influence of enzyme systems of the body. This distinguishes Coenzyme Q10 from other antioxidants, which, in fulfilling its function irreversibly oxidized themselves, requiring additional administration [1].

Clinical studies of recent decade showed Coenzyme Q10 effectiveness in treatment of coronary artery disease, hypertension and chronic fatigue syndrome. Experimental studies have demonstrated preventive and therapeutic effect during reperfusion syndrome [22, 27, 29].

After treatment patients with unstable angina showed a significant decrease in the level of tyrosine in serum that can be interpreted as a compensatory response, as this may indicate an increase in the catabolism of tyrosine to synthesize Coenzyme Q10 ($p < 0.01$).

Patients with unstable angina compared with healthy individuals have significantly reduced cysteine levels in the blood serum ($p < 0.01$). In body hydrogen sulfide (H_2S) is synthesized from L-cysteine is [29]. Recent studies have shown that hydrogen sulfide, known as third gaseous signaling molecule close to NO and CO, plays an important role in the regulation of cardiovascular system. It causes endothelium dependent vascular relaxation [31], prevents inflammation [25], it stimulates angiogenesis [26]. Cardioprotection effect under ischemic myocardial damage observed when applying a wide range of doses of exogenous donors of H_2S [24, 27], but about endogenous H_2S there is less information. It is proved that the introduction of L-cysteine in conditions of ischemic damage to the heart reduces myocardial infarction zone and stimulates antioxidant defense system [30], but the conversion of L-cysteine to H_2S - is not the only pathway of amino acid metabolism and it is not known by which mechanism it is carried out a protective effect. Total action of irreversible inhibitor of cystathionine lyase and L-cysteine is preventing the formation of mitochondrial pores, as evidenced by a decrease in the release of mitochondrial factors. This indicates a more efficient utilization of oxygen by the myocardium. We know that the integrity of mitochondrial membranes ensure the effectiveness of the antioxidant defense system - enzymes superoxide dismutase, catalase, and glutathione.

After treatment in blood serum of patients with unstable angina; cysteine content was significantly increased and it becomes significantly more than in the CG ($p < 0.05$ in both cases). It is perhaps compensatory, defensive reaction, because the increase of cysteine makes it possible to increase the synthesis of H_2S.

5. Conclusions

1. In Unstable Angina patients compared to the CG showed a significant decrease amount of in the vast majority of nonessential amino acids (glutamic acid, proline, serine, taurine, cysteine), which indicates an increase in its catabolism.
2. Patients with unstable angina under the influence of anti-anginal therapy with L-arginine takes a significant reduction of some AA in the blood serum, which is probably due to the increased use of amino acids for the synthesis of biologically active substances that generally have protective properties (alanine - pyruvic acid, aspartic acid - asparagine, glycine –glutathione, glutamine - glutathione, serine - serine protease and immunoglobulins, tyrosine - CoenzymeQ10).
3. For patients with unstable angina antianginal therapy including L-arginine caused a significant increase in the content of ornithine, which can be regarded as a protective response, since ornithine participates in the urea cycle and in patients after treatment showed significantly lower content of ammonia in the serum.
4. After treatment in blood serum of patients with unstable angina the content of taurine significantly increases, which is likely to facilitate the entry of the AA into the myocardium as a cardioprotector.
5. Antianginal therapy with inclusion of L-arginine in patients with unstable angina leads to a significant increase in the serum content of cysteine as a substrate for the synthesis of hydrogen sulfide, it can be considered as a compensatory response to myocardial ischemia.

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