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## RESEARCH ARTICLE

# THE INFLUENCE OF THE ADDITIONAL USAGE OF L-ARGININE ON THE FACTORS OF VASODILATION AND THE CLINICAL DATA, COMPLICATED WITH CARDIAC DECOMPENSATION WITH REDUCED AND PRESERVED FRACTION OF THE LEFT VENTRICLE THAT PATIENTS WITH STABLE CORONARY HEART DISEASE HAVE

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### ABSTRACT

**Introduction:** The endothelial dysfunction is one of the most difficult forms of vascular malformation. The dominant ferment, that provides the synthesis NO in the blood-making stream, is the endothelial NO-synthase, that is produced on the endothelium and plays an important role in the basic level NO support (Erdei *et al.*, 2014; Cwynar *et al.*, 2015). It is proved that the reduction of the activity eNOS leads to the decrement NO production and is one of the key elements of pathogenesis coronary heart disease (CHD) (Zaremba, 2012).

The aim of the research: to estimate the influence of the additional usage of L-arginine hydrochloride on the factors of vasodilation and the clinical data, complicated with cardiac decompensation with impaired and reserved ejection fraction of the left ventricle that patients with stable CHD have.

**Materials and methods:** To achieve the aim of the research the full medical observation with 40 CHD patients was held (28 men and 12 women, the average age is 68,80±0,90 years), who were in the heart disease department for the patients with rhythm disturbance Vinnytsya regional cardiovascular pathology centre (Ukraine).

**Results:** After the comparing the levels of the vasodilatation factors of the healthy people (the control group) with the information that the patients with the stable CHD, complicated with HF with impaired and reserved LV EF, the certain difference between the markers of the levels eNOS, nitrites and nitrates in the blood serum ( $p < 0.01$ ), that deposes the increasing of the endothelial dysfunction. Similar results were obtained in patients 2 groups. , the patients with the decreasing LV EF and the progressing HF had the certain decreasing of the level eNOS, nitrites and the nitrates in the blood serum, that deposes the negative difficulties of the endothelial function. The analogical information got after the standard complex therapy HF during 10 days with the additional usage L-arginine hydrochloride at a dose 100 ml 4,2 % intravenous, the patients of the first group have the following level eNOS 664,80±85,68 pg/ml, the patients of the second group – 837,81±49,98 pg/ml ( $p < 0.01$ ), that deposes the positive effect of the additional usage of L-arginine hydrochloride. After the complex standard treatment during 10 days tolerance to the physical work in the patients I and II groups increased. The results of the research proves that the patients with the stable CHD, complicated with HF with decreased and reserved LV EF after the usage of "Tivortin" 100 ml 4,2 % intravenous during 10 days influenced the increasemnet of FC HF.

**Conclusions:** After the comparing the levels of the vasodilatation factors of the healthy people with the information that the patients with the stable CHD, complicated with cardiac decompensation with impaired and reserved fraction of the left ventricle, the certain difference between the markers of the levels eNOS, nitrites and nitrates in the blood serum, that deposes the increasing of the endothelial dysfunction. After the treatment heart failure during 10 days with the additional usage L-arginine hydrochloride at a dose of 100 ml 4,2 % intravenous, the level of the vasodilatation increased, particuar the endothelial NO-synthase not only in the patients with stable CHD, with impaired and reserved fraction of the left ventricle. The results of the research proves that the increasing levels of vasodilators in the blood serum influences the decreasing of the clinical symptoms heart failure, that deposes the effectiveness of the following therapy.

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### INTRODUCTION

The endothelial dysfunction is one of the most difficult forms of vascular malformation. Anti-inflammatory and antiatherogenic characteristics of the vessel wall are determined by the stable state of endothelium, its ability to be produced from L-arginine and produce the biologically active compound - nitrogen oxide (NO) (Netyazhenko *et al.*, 2016). NO is the strong vasodilator and cardiotropic agent.

It is thought that the feeble production and/or accelerated degradation NO play an important role not only in increasing the arterial tension, but in the development of such complications as: apoplectic attack, heart attack, myocardial infarction and also congestive heart failure (HF) (Voronkov *et al.*, 2004). The dominant ferment, that provides the synthesis NO in the blood-making stream, is the endothelial NO-synthase, that is produced on the endothelium and plays an important role in the basic level NO support (Erdei *et al.*,

2014; Cwynar *et al.*, 2015). It is thought that L-arginine under the influence of the endothelial NO-synthase is changed into NO and citrulline (Netyazhenko and Malchevskaya, 2016; Shlyakhto *et al.*, 2010). It is proved that the reduction of the activity eNOS leads to the decrement NO production and is one of the key elements of pathogenesis coronary heart disease (CHD) (Zaremba, 2012).

### The aim of the research

To estimate the influence of the additional usage of L-arginine hydrochloride on the factors of vasodilation and the clinical data, complicated with cardiac decompensation with impaired and reserved ejection fraction of the left ventricle that patients with stable CHD have.

## MATERIALS AND METHODS

To achieve the aim of the research the full medical observation with 40 CHD patients was held (28 men and 12 women, the average age is 68,  $80 \pm 0,90$  years), who were in the heart disease department for the patients with rhythm disturbance Vinnytsya regional cardiovascular pathology centre (Ukraine).

### The research inclusion criteria

Patients with stable CHD, that changed HF I-III functional class (FC) after the patient's agreement. *The exclusionary criteria:* HF IV FC for NYHA; the terms up to 3 months from the beginning of the heart attack or insult; CA- i AV-blocks II-III stages, implant artificial pacemaker or implantation; the difficult diseases of the respiratory system, kidneys, liver with liver decompensation, anemic states with the hemoglobin level  $90,0$  g/l and lower; malignant tumors and difficult neurotic problems. The diagnosis and FC HF were made based on the clinical, laboratorial and instrumental criteria, according to the recommendations of the European Association of Cardiologists and the Ukrainian Association of Cardiologists (2012; 2016) (ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012). The diagnostics and the treatment of the clinical forms were done according to the order of the Ukrainian Ministry of Public Health № 152 from 02.03.2016 (Mandate of the Ministry of Health of Ukraine from, 2016); the functional class - according to the classification NYHA. To define FC HF all the patients were tested with the help of 6-minutes-pace. The distance, that every patient could overcome during 6 minutes, was measured. The patient was suggested to choose the most comfortable pace and go till the end of the hall and back to the start point, continuing to walk during 6 minutes. Patients were allowed to pace themselves and to have a rest, walking again after that. Depending on the distance for 6 minutes, there was defined the following: I FC HF - 426-550 m, II FC HF - 300-425 m, III FC HF - 150-299 m, IV FC HF - 149 m and less. The arterial hypertension was found in 34 (85,00 %) patients. The systolic blood pressure (BP) was in average  $142,40 \pm 5,01$  mm Hg., diastolic BP -  $88,30 \pm 2,95$  mm Hg. All the patients were divided into 2 groups: the first group contained patients with stable CHD and HF with decreased left ventricular ejection fraction (LV EF) ( $< 40,0$  %) ( $n = 20$ ); the second group - patients with stable CHD and HF with reserved EF LV ( $> 50,0\%$ ) ( $n = 20$ ). Beside the complex of clinical-laboratorial and instrumental observations, that meet modern requirements, the patients got the qualitative number of vasodilation markers

- nitrites ( $\text{NO}_2^-$ ) and nitrates ( $\text{NO}_3^-$ ); the endothelial NO-synthase (eNOS). The NO method was based on the photolorimetric analysis of the optical dense of  $\text{NO}_2^-$  with the Griss reagent after the methyl cyanide (Mandate of the Ministry of Health of Ukraine from, 2016). Before that nitrates were restored up to the nitrites with the help of zinc dust and hydrides of nitrogen, they defined the overall content of the metabolites NO according to the reaction with the reactor I.P. Griss. The individual content of the nitrates ( $\text{NO}_3^-$ ) defined the difference between the overall content of metabolites and the content of nitrites ( $\text{NO}_2^-$ ) in the blood serum. The content of eNOS in the blood serum defined the immune method by means of "Nitric Oxide Synthase 3, Endothelial (eNOS) Human ELISA Kit" (Cloud-Clone Corp, the USA). Echocardiography (EchoCG) were held in M and B modes with the help of impulsive myocardial Doppler imaging by means of the equipment SONOACE ("Medison") with the American cardiological Association recommendations. Blood for the research was taken twice: before the hospital treatment and after the standard therapy with the additional usage L-arginine hydrochloride at a dose of 100 ml 4,2 % ("Tivortin", YuriyaFarm, Ukraine) inside venous during 10 days. The standard therapy HF contains:  $\beta$ -adrenergic blockers (carvedilol - 25 mg/day, or bisoprolol - 5-10 mg/day); inhibitor of the angiotensin-transformed ferment (perindopril - 5-10 mg/day) or blockers of angiotensin receptors (valsartan - 80-160 mg/day); diuretics (torsemide - 10-20 mg/day, spironolactone - 25 mg/day); antiplatelets (acetylsalicylic acid - 75 mg/day); statins (atorvastatin - 20 mg/day). The statistical analysis was held with the help of the standard statistical packet STATISTICA 6, 0.

### The results of the research and their discussions

The availability of L-arginin for the endothelial NO-synthase nowadays is accepted as one of the main conditions of the production of the endothelial NO. In the research J. S. Pollock *et al.* (1991) it was found out that L-arginine hydrochloride has a positive influence on the functions of endothelium despite the reason for the decreasing of the bioavailability NO [12, 17]. We learned the influence of the additional usage of L-arginine hydrochloride on the content of eNOS and the endothelial NO-synthase in the blood serum that the patients with stable CHD have in comparison with those who are healthy (Table 1). After the comparing the levels of the vasodilatation factors of the healthy people (the control group) with the information that the patients with the stable CHD, complicated with HF with impaired and reserved LV EF, the certain difference between the markers of the levels eNOS, nitrites and nitrates in the blood serum ( $p < 0.01$ ), that deposes the increasing of the endothelial dysfunction. Also, we learned the influence of the additional usage of L-arginine hydrochloride on the content of eNOS and the endothelial NO-synthase in the blood serum that the patients with stable CHD have, complicated with cardiac decompensation with impaired and reserved LV EF, in comparison with those who are healthy (Table 2). After the comparing the levels of the vasodilatation factors of the healthy people (the control group) with the information that the patients with the stable CHD, complicated with cardiac decompensation with impaired and reserved LV EF heart discharge, the certain difference between the markers of the levels eNOS, nitrites and nitrates in the blood serum ( $p < 0.01$ ), that deposes the increasing of the endothelial dysfunction.

**Table 1. The influence of the additional usage of L-arginine hydrochloride on the factors of vasodilation, complicated with cardiac decompensation with reduced left ventricular ejection fraction in comparison with healthy patients (M±m)**

Marker	Healthy people (control group) n = 10	Patients with HF with decreased LV EF group 1, n = 20	
		Before the treatment	After the treatment
eNOS, pg/ml	731,79±84,63	371,98±29,30*	664,80±85,68
Nitrites +nitrates, mmol/l	26,08±0,92	16,73±0,52*	17,25±1,29#
Nitrites, mmol/l	6,31±0,18	4,20±0,25*	4,50±0,52#
Nitrates, mmol/l	19,77±0,90	12,54±0,61*	12,75±1,32#

**Remarks:** ● – comparison of the patients' information with the healthy people's data ( $p < 0.01$ ); # - comparison of the patients' information with the healthy people's data after the treatment ( $p < 0.01$ ).

**Table 2. The influence of the additional usage of L-arginine hydrochloride on the factors of vasodilation, complicated with cardiac decompensation with reserved left ventricular ejection fraction in comparison with healthy patients (M±m)**

Marker	Healthy people (control group) n = 10	Patients with HF with reserved LV EF group 2, n = 20	
		Before the treatment	After the treatment
eNOS, pg/ml	731,79±84,63	555,70±22,53	837,81±49,98
Nitrites +nitrates, mmol/l	26,08±0,92	19,54±0,63*	21,08±0,87#
Nitrites, mmol/l	6,31±0,18	4,98±0,17*	5,64±0,33
Nitrates, mmol/l	19,77±0,90	14,55±0,59*	15,44±0,86#

**Remarks:** ● – comparison of the patients' information with the healthy people's data ( $p < 0.01$ ); # - comparison of the patients' information with the healthy people's data after the treatment ( $p < 0.01$ ).

**Table 3. Comparative characteristics of the impact the additional use of L-arginine hydrochloride on factors vasodilation in patients with stable coronary artery disease complicated by heart failure with reduced and preserved left ventricular ejection fraction before and after treatment (M±m)**

Marker	Patients with HF with decreased LV EF group 1, n = 20		Patients with HF with reserved LV EF group 2, n = 20	
	Before the treatment	After the treatment	Before the treatment	After the treatment
eNOS, pg/ml	371,98±29,30	664,80±85,68	555,70±22,53*	837,81±49,98#
Nitrites +nitrates, mcol/l	16,73±0,52	17,25±1,29	19,54±0,63*	21,08±0,87#
Nitrites, mmol/l	4,20±0,25	4,50±0,52	4,98±0,17*	5,64±0,33
Nitrates, mmol/l	12,54±0,61	12,75±1,32	14,55±0,59*	15,44±0,86#

**Remarks:** ● – comparison of the patients' information with the healthy people's data ( $p < 0.01$ ); # - comparison of the patients' information with the healthy people's data after the treatment ( $p < 0.01$ ).

**Table 4. The dynamics of the functional classes of the cardiac decompensation according to the classification NYHA in patients with stable coronary artery disease complicated by heart failure with reduced and preserved left ventricular ejection fraction before and after treatment**

FC HF NYHA	Marker	Patients with HF with decreased LV EF group 1, n = 20		Patients with HF with reserved LV EF group 2, n = 20	
		Before the treatment	After the treatment	Before the treatment	After the treatment
I	n	-	1	3	6
	%	-	5,0	15,0	30,0
II	n	4	6	9	12
	%	20,0	30,0	45,0	60,0
III	n	16	9	8	2
	%	80,0	45,0	40,0	10,0
Overall total	n	20	20	20	20
	%	100,0	100,0	100,0	100,0

In 2009 the results of the meta-analysis of 13 random researches, that were held with the aim of learning the effect L-arginine hydrochloride on the functional state of the endothelium. In these researches the L-arginine hydrochloride effect was learned in the hypercholesteremia, stable angina, peripheral arteria diseases and CHF (the duration of the treatment is from 3 up to 6 months). The meta-analysis showed that the prescription of L-arginine really increases the display of the arteries vasodilatation in comparison with the markers during the taking placebo, that deposes the improvement of the endothelium function (Tashchuk, 2016). Also, we learned the influence of the additional usage of L-arginine hydrochloride on the content of NO and the endothelial NO-synthase in the blood serum that the patients with stable CHD have, complicated with cardiac decompensation with impaired and LV FE heart discharge, in comparison with those who are healthy (Table 3).

From the tab.3 the patients with the stable CHD, complicated with HF with decreased LV EF, in comparison with the patients with stable CHD, complicated HF with the reserved LV EF before the treatment, the certain decreasing of the levels eNOS, nitrites, nitrates and the overall level of nitrites and the nitrates in the blood serum ( $p < 0.01$ ), that deposes the decreasing of the vasodilatated factors that has a negative influence on the disease. Thus, the patients with the decreasing LV EF and the progressing HF had the certain decreasing of the level eNOS, nitrites and the nitrates in the blood serum, that deposes the negative difficulties of the endothelial function. The analogical information got after the standard complex therapy HF during 10 days with the additional usage L-arginine hydrochloride at a dose 100 ml 4,2 % intravenous, the patients of the first group have the following level eNOS 664,80±85,68 pg/ml, the patients of the second group – 837,81±49,98 pg/ml ( $p < 0.01$ ), that deposes the positive effect of the additional usage of L-arginine hydrochloride.

Patients with the stable CHD, complicated with HF with impaired and reserved fracture of the left ventricle heart discharge, the learning of the influence of the additional usage of L-arginine hydrochloride on the clinical information are shown on the Table 4. After the complex standard treatment during 10 days tolerance to the physical work in the patients I and II groups increased. The results of the research proves that the patients with the stable CHD, complicated with HF with decreased and reserved LV EF after the usage of "Tivortin" 100 ml 4,2 % intravenous during 10 days influenced the increasemnet of FC HF. The researches of the last century showed that the peroral and the infusion therapy with L-arginine improves endothelial arteries vasodilatation in the patients CHD (Creager *et al.*, 1992). In the patients with arterial hypertension L-arginine hydrochloride decreases BP and the general peripheral vascular resistance, and also enlarges cardiac output (Kugiyama *et al.*, 1996). The results of the research proves that the increasing levels of vasodilators in the blood serum influences the decreasing of the clinical symptoms HF, that should be noticed in the process of choosing the methods of treatment of such patients.

### Conclusions

- After the comparing the levels of the vasodilatation factors of the healthy people with the information that the patients with the stable CHD, complicated with cardiac decompensation with impaired and reserved fracture of the left ventricle, the certain difference between the markers of the levels eNOS, nitrites and nitrates in the blood serum, that deposes the increasing of the endothelial dysfunction.
- After the treatment heart failure during 10 days with the additional usage L-arginine hydrochloride at a dose of 100 ml 4,2 % intravenous, the level of the vasodilatation increased, particuar the endothelial NO-synthase not only in the patients with stable CHD, with impaired and reserved fracture of the left ventricle.
- The results of the research proves that the increasing levels of vasodilators in the blood serum influences the decreasing of the clinical symptoms heart failure, that deposes the effectiveness of the following therapy.

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