KAPITEL 6 / *CHAPTER 6* [6]
L-ARGININE SUPPLEMENTATION IN ANTIHYPERTENSIVE THERAPY: A NOVEL APPROACH TO ENDOTHELIAL AND METABOLIC CORRECTION IN INSULIN-RESISTANT PATIENTS

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Introduction

Cardiovascular diseases (CVD) - hold one of the leading places in the causes of death in Ukraine [1]. Decisive role in increasing of cardiovascular pathology is being played by the negative ”acqusions” of the modern society - sedentary lifestyle, chronic stress and increasing of caloric value of the food. Those modifying risk factors lead to incessant increasing to arterial hypertension (AH),dyslipidemia, adiposity and insulin resistance [2, 3].

Nowadays AH is considered as a endothelium dysfunction (ED) condition, that is accompanied by constriction of vascular smooth muscles, increasing of left ventricle emission resistance and predisposition to atherosclerosis [3, 4].

Endothelial dysfunction of the vessels is pathogenetically connected with insulin resistance (IR) development, that is observed in a significant number of patients with AH and lies in the basis of metabolic syndrom [5, 6]. The accumulated experimental and clinical material together with epidemiological researches, that showed increase of insulin level in patients with AH, certainly indicate that IR is an important pathogenetical link of AH [7].

IR-is an insufficient biological responce of the cells to insulin action with its sufficient concentration in blood [8]. Causal connection of endothelial dysfunction (ED) and IR still are disputable. In numerous researches it has been demonstrated that ED is the consequence of those mechanisms, that lie in the basis of IR - hypeglycemia, arterial hypertension (AH) and dyslipidemia. With hyperglycemia a protein kinase-C enzyme is being activated in endothelial cells, that increases vascular cells permeability

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for proteins and breaches endothelium dependent vasodilatattion (EDV) [9]. Besides this, hyperglycemia activates the processes of lipid pereoxidation, which products inhibit vasodilatory function of endothelium. With AH, a defection of endothelial cells architectonics, increase production of vasoconstrictor endothelin-1, vascular remodelling with hardening of blood vessels takes place. Thus, the mechanisms mentioned above reduce EDV while increasing the permeability of endothelium and adhesion molecules expression [10]. Other researchers consider that ED leads to IR development in the consequence of defection of transendothelial transportation of insulin [11].

With no doubt, IR and ED , including production of NO, are closely connected with each other and build a pathological ”vicious circle”, that leads to metabolic and cardiovascular diseases. Despite the fact that a lot of causal connections in pathogenesis of ED are still not found out , it is an unconditional fact, that ED is the first link in atherosclerosis development, that is connected with IR syndrom.

In this direction, in our opinion, it is perspective to study the influence of natural predecessor NO-L-arginine on the functional condition of vascular endothelium, and also on carbohydrate and lipid metabolism of the patients with hypertonic disease accompanied by insulin resistance.

L-arginine (α-amino-δ-huanido valerian acid) - conditionally essential acid, that is an active and versatile cell regulator of numerous vital body functions. L-arginine is a substarate for NO-synthase-enzyme, that catalyzes synthesis of NO in endothelials [12].

Material and research methods.

For the basis of this reserach, the examination results of 37 patients with AH II stage, chronic heart failure (CHF) 0-I stage, I-II functional classes (FC), aged from 60-88 years old (the average age was (77,3±0,8 years) and concomitant insulin resistance were taken. All the patients were males.

Criteria for exclusion from the research: symptomatic arterial hypertensions, clinical and electrocardiographic symptoms of CHD, dysfunctions of sinoartrial and atrioventricular conductance of II-III stage, auricle fibrillation, frequent ventricular and

supraventricular beats, AH of I and III stages, abdominal adiposity of II and III stages, CHF of II-III stages, III-IV FC, glucose level in blood plasma fasting ≥ 6,1 mmol/l, diabetes, chronic obstructive lungs diseases, chronic diseases of alimentary canal and kidneys in the acute phase, endocrinological diseases.

To diagnose insulin resistance HOMA-index (Homeostasis model assessment) has been used, that has been calculated according to the formula:

HOMA = insulin level in blood fasting (mIU/ml) multiplied by glucose level in blood fasting (mmol/l) and divided by 22,5. A normal index has been considered HOMA-index not greater than 2,77 [13].

Endothelium dependent vasodilatation (EDV) has been determined with the help of D. Celemajer test. The evaluation of flow induced vasodilatation has been held by means of measuring artery diameter in the phase of reactive hyperemia (after vascular decompression). EDV was defined as a ratio of changes in the value of the diameter of brachial artery after tests held with reactive hyperemia to its value in the tranquility state. A normal reaction of brachial artery has been considered to be its dilatation on the background of test with reactive hyperemia more than 10% from its original value. Dilatation of less than 10% witnessed of violations of EDV. A test with peropherialvasodilator nitroglycerin was held after the patient had spend 15 minutes in the state of tranquility. Endothelium not dependant vasodilatation (ENDV) was calculated as a ratio of the artery diameter change after taking nitroglycerin to its original (initial) value. A normal reaction of brachial artery has been considered to be its dilatation to more than 20%. In all observation groups, we have also measured the speed of bloodflow in the brachial artery in the state of tranquility and on the background of test with hyperemia (V, m/s). The ratio of change of the blood flow speed in the brachial artery after the test with reactive hyperemia to its value in the state of tranquility was also determined.

According to the scheduled design of research, all the patients with AH of II stage received combined antihypertensive therapy with an inhibitor of angiotensin converting enzyme lisinopril in the dosage of 5-20 mg/day, hypolipidemic therapy with atorvastatin in the dosage of 10 mg per day. While examining prescribed doses of

antihypertensive medication, that were used to reach the target levels of BP, in most cases the usage of lisinopril in the dosage of 10 mg per day and amlodipine in the dosage of 5 mg per day took place. The average dosage of lisinopril in the patients with AH of II stage was (12,3 + 0,8) mg,the average dose of amlodipine (6,1 + 0,3) mg.

Among the patients with AH, a group of patients (19 people) was separated, that besides the above mentioned treatment scheme, additionally received infusive and oral L-arginine forms. In the period of 12-14 days (the period of hospital stay), the patients were daily infused with 100 ml of **Tivortin** solution (4,2% solution of L-arginine chloride). After checking out of the hospital, the patients orally took 40 minutes before the meal 20 ml of **Tivortin aspartat** solution (4 gramms of L-arginine)(4 measuring spoons) twice a day. The treatment course of infusive and oral forms – 3 months (90 days). The evaluation of effectiveness was held after 3 months from the beginning of the prescribed treatment.

Static processing of the research results was conducted with the help of variation statistics mehtods, using the programmme StatSoft "Statistica" v. 6.0. The majority of the indicators bore abnormal distribution (the distribution type was determined with the help of Shapiro-Wilks test), that's why we used the methods of non-parametric statistics. The research results were represented as median and interquartile swing (25-75 percentiles). The differnce of $p<0,05$ was considered to be statically probable.

The results and discussion of them

The characteristics of endothelial functions of the vessels of the examined patients before and 3 months after the basic therapy (lisinopril+amlodipine+atorvastatin) and the therapy with additional inclusion of L-arginine (lisinopril+amlodipine+atorvastatin +L-arginine) are shown in the Table 1.

It's also necessary to mention, that the majority of examined patients had explict endothelial dysfunction of the vessels as a considerable lowering of EDV with a formation of mainly vasoconstrictive reaction to the test with reactive hyperemia. The detected defections don't contradict the majority of the reserches results [14, 15].

Table 1 - The dynamics of endothelial functions of the vessels of the patients with hypertonic disease with insulin resistance under the influence of different treatment schemes

Indicators	Basic therapy (n=18)	Basic therapy+L-arginine (n=19)	Result after 3 months
EDV, %			
Original value	-3,5 (-7,4; 3,8)	-4,4 (-7,5; 4,8)	
After 3 months	3,7 (0; 9,9)	5,4 (4,4; 7,7)	
Dynamics, %	63,1 (-13,1; 108,0)	97,9 (68,9; 202,8)	**0,036**
d-(o-3)	**<0,0001**	**<0,0001**	
ENDV, %			
Original value	16,5 (15,7; 18,4)	17,1 (16,2; 17,9)	
After 3 months	17,5 (15,8; 18,3)	17,5 (16,7; 17,9)	–
Dynamics, %	2,2 (-11,1; 14,1)	0 (-2,4; 12,0)	
d-(o-3)	0,34	0,95	
Dynamics V to RHT, %			
Original value	40,2 (34,4; 50,3)	42,4 (36,4; 57,1)	
After 3 months	42,4 (38,4; 48,3)	57,1 (41,7; 60,3)	**0,026**
Dynamics, %	6,2 (-13,4; 23,2)	17,1 (2,0; 30,5)	
d-(o-3)	**0,042**	**<0,0001**	
The character of brachial artery reaction to the test with reactive hyperemia			
Normal			
Original value	0	0	
After 3 months	25,0 %	17,6 %	
Dynamics, %	25,0	17,6	
d-(o-3)	0,10	0,19	
Reduced			
Original value	37,5 %	35,3 %	
After 3 months	43,8 %	82,4 %	**0,006**
Dynamics, %	6,3	47,1	
d-(o-3)	0,93	**0,020**	
Vasoconstriction			
Original value	62,5 %	64,7 %	
After 3 months	31,2 %	0	**0,032**
Dynamics, %	-31,3	-64,7	
d-(o-3)	0,20	**0,0003**	

Notes:

1. EDV- endothelium dependent vasolidation, ENDV- endothelium not dependent vasolidation, V-the speed of blood flow in the brachial artery, RHT –reactive hyperemia test.
2. d(o-3) –certainty of the results comparing the original value of the indicators with the value of 3rd month, calculated according to the criterium of Wilkocson
3. d-certainty of difference of characteristics distribution frequence,calculated according to the criterium of $\chi 2$.

It can also be noted, that ENDV was lowered in all the groups of the examined patients. It should be mentioned, that a dysfunction of normal vasodilating reaction to nitroglycerin of the patients with AH and IR, makes it possible that a defected reaction of smooth muscles cells of the vesssels to nitrovasolidators possibly take part in

endothelium dysfunction development. Some researches explain that by early "aging" of the vessels of the patients with IR with vascular cytoarchitecnonics [16, 17]. In the patients with AH accompanied by IR, EDV significantly improved under the influence of different therapy schemes after 3 months of observation. In 3 months, EDV in the selected groups of the patients under the effect of basic therapy scheme increased by 63,1%, and with additional prescription of L-arginine to 97, 9%.

Increase, induced by the blood flow of EDV, while taking 6gr per day of L-arginine was confirmed by J.P. Lekakis et al. [18] in prospective randomized double blind study with the participation of 35 patients with AH. Taking L-arginine significantly increased dilatation of brachial artery, due to blood flow (1,7±3,4% compared to з 5,9±5,4%; d = 0,008). In a research, held by A. Palloshi et al., oral intake of L-arginine 6gr per day by the patients with microvascular stenocardia and AH, significantly increased EDV and the level of cyclic GMP [19].

The changes in the basic parameters of carbohydrate metabolism under the influence of antihypertensive therapy with lisinopril and amplodipine and hypolipidemic therapy with atorvastatin and the scheme with additional prescription of L-arginine are shown in the Table 2.

Table 2 – Dynamics of carbohydrate metabolism parameters of the patients with hypertonic disease with insulin resistance under the influence of different treatment schemes

Biochemical parameters	**Basic therapy (n=18)**	**Basic therapy+ L-arginine (n=19)**	**p**
Glucose mmol/l Original value After 3 months Dynamics, %	 4,95 (4,55; 5,75) 5,00 (4,60; 5,45) 2,0 (-5,6; 4,9)	 5,10 (4,60; 5,40) 4,90 (4,60; 5,50) -2,1 (-5,2; 3,1)	**After 3months** 0,87
Insulin мОД/ml, Original value After 3 months Dynamics, %	 11,45 (10,75; 12,20) 11,20 (10,50; 11,70) -3,2 (-10,2; 1,2)	 11,40 (10,60; 12,20) 11,00 (10,20; 11,90) -3,7 (-14,5; 2,5)	**After 3 months** 0,78
HOMA Original value	 2,79 (2,77; 2,88)	 2,80 (2,78; 2,86)	

After 3 months Dynamics, %	2,71 (2,53; 2,82) -4,1 (-9,6; 2,4)	2,63 (2,52; 2,77)* -6,1 (-13,8; -0,3)	**After 3 months** 0,26

Notes:
1.Symbol: *HOMA* (*Homeostasis model assessment*) – index, that is used for determination of insulin resistance.
2. *<0,05 - certainty of the results comparing the value of the parameters of the 3rd month to the original value , calculated according to the criterium of Wilkocson.
3.d-certainty of differences of parameters dynamics between the selected groups of patients for the 3rd month, evaluated according to the criterium of $\chi 2$.

The research results of the changes in carbohydrate metabolism under the influence of different schemes of combined antihypertensive and hypolipidemic therapy demonstrated significant lowering of *HOMA*-index after 3 months of treatment only in the patients with AH with insulin resistance, whose treatment scheme additionally included L-arginine (d<0,05). The dynamics of changes in the level of glucose and insulin of the selected groups of patients with AH didn't change significantly and didn't lead to verified lowering of the above-mentioned parameters for 3 months of observation period.

It's also worth mentioning, that increasing tissue sensitivity to insulin under the effect of L-arginine is also noted in other researches. Thus, P. Lucotti et al. [20], in randomized blind study, with the participation of 64 patients with CVD without diabetes after aortic shunting with taking of L-arginine orally in the dose of 6,4 gr. per day during 3 months, found out that EDV (d<0,01) increased, insulin resistance lowered (d<0,05) and the level of Adiponectin increased (d<0,01). In a research held by Piatti P.M. et al., peroral intake of L-arginine 9gr. per day during 1 month by the patients with diabetes of 2nd type led to significant increase of blood flow in forearm (to 36%), normalization of initially reduced level of cyclic GMP, lowering of systolic BP by 14% and improvement of sensibility to insulin [21].

It should also be noted, that in the process of treatment of the patients with medications Tivortin and Tivortin aspartat only one (out of 19!) patients had the side effects, i.e. light dyspeptic disorders, which were really slight and didn't require cancellation of the medication, that indicates to good tolerability of these drugs.

Conclusions

1. Combination of antihypertensive and hypolipidemic therapy atorvastatin and gradual including of L-arginine by intravenously-oral way in the treatment of patients with hypertonic disease and accompanied insulin resistance, helped to improve the endothelial function of the vessels, namely statically significant improvement of endothelium dependent vasodilatation, compared to the group of patients, whose treatment scheme included only lisinopril, amplodipine та atorvastatin. In the process of treatment with L-arginine medications, there was significant lowering of *HOMA*-index and the level of triglycerides, in comparison with the group of the patient, who only got basic treatment, which indicates to improvement of carbohydrate and lipid metabolism under the influence of L-arginine medications.

2. In a therapy with L-arginine medications, the side effects of one (out of 19) patients, point to the safety of its usage by the patients with AH and insulin resistance.

3. The results of the clinical research give us a possibility to recommend phased including of L-arginine by intravenously-oral way in a comprehensive treatment of the patient with hypertonic disease and insulin resistance.