Shtanko V. A., Romanchuk A. P., Marish M. Y., Tesluk G. B. L-Arginine and arterial hypertension: antihypertensive and metabolic effects. Journal of Health Sciences. 2014;4(16):179-186. ISSN 1429-9623 / 2300-665X.
http://journal.rsw.edu.pl/index.php/JHS/article/view/2014%3B4%2816%29%3A179-186
https://pbn.nauka.gov.pl/works/545986

The journal has had 5 points in Ministry of Science and Higher Education of Poland parametric evaluation. Part B item 1089. (31.12.2014).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 15.11.2014. Revised 05.12.2014. Accepted: 25.12.2014.

L-ARGININE AND ARTERIAL HYPERTENSION: ANTIHYPERTENSIVE AND METABOLIC EFFECTS

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Resume. The effectiveness of antihypertensive treatment remains at a low level despite of numerous antihypertensives. Nitric oxide (NO) plays an important role in the pathogenesis of arterial hypertension (AH). It is synthesized from L-arginine in the presence of endothelial NO-synthase but the practical use of the above mentioned amino acid in the treatment of AH remains uncertain. In this study a total of 80 adult patients (men and women in equivalent amounts) with AH II stage were recruited. The whole group of patients was divided into 2 subgroups according to the prescribed antihypertensive pharmacotherapy: 1st subgroup (n=40) used Valsartan 0.08 g *per os* once a day in the morning + Amlodipinum 0.005 g *per os* once a day in the evening; 2nd subgroup (n=40) in addition to the above mentioned medicines used L-arginine 1.0 g three times a day before meal. To estimate the efficacy of treatment and its metabolic effects were evaluated the following parameters: systolic and diastolic blood pressure, glucose, total cholesterol, high- and low- density lipoproteins, triglycerides. The period of clinical observation was 30 days.

All patients had different neurological complaints, such as: anxiety, headache, loss of concentration, insomnia, dizziness, fatigue. At the end of clinical observation their quantity and expressiveness decreased, especially in the 2nd group. One patient even required lower dose of L-arginine (2.0 g/day) because of the significant daytime sleepiness. After the correction of pharmacotherapy this complaint disappeared. In 5 patients the use of L-arginine before meal caused gastrointestinal disorders, such as nausea, flatulence and epigastric discomfort. That is why they began to use this medicine during or after meal. Such change in the treatment didn't reduce the effectiveness of L-arginine.

In 30 days the levels of systolic and diastolic blood pressure decreased, especially in the 2nd group of comparison ($p<0.05$). The effectiveness of antihypertensive therapy in the 1st group was

78%, the optimal levels of blood pressure were achieved after 12-14 days of treatment. Patients of the 2nd group achieved stable levels of blood pressure in 10-12 days, but in 10 patients the dose of Amlodipin was reduced to 0.0025 mg/day because of the threat of hypotension.

In this study had not found any effects of L-arginine on levels of glucose, total cholesterol, high- and low- density lipoproteins, triglycerides ($p>0.05$). Absence of significant effect of L-arginine on the levels of blood glucose and lipids allows to use it in patients with different risk factors or comorbid pathology.

Key words: arterial hypertension, nitric oxide, L-arginine.

Introduction. Arterial hypertension (AH) is one of the most common diseases, which significantly determines the structure of morbidity and mortality from cardiovascular pathology. Despite of numerous researches antihypertensive pharmacotherapy often remains ineffective. This can be explained by the polygenic inheritance, unknown molecular and biochemical mechanisms of the disease.

Now is discussed the role of nitric oxide (NO) in the etiopathogenesis of AH. This factor is synthesized from L-arginine in the presence of endothelial NO-synthase [1]. It has multiple paracrine effects and may influence the function of cardiovascular, nervous and immune system. NO-insufficiency causes endothelial dysfunction and associated with it vasoconstriction, thrombosis, vascular wall inflammation, oxidative stress and smooth muscle cells proliferation [2]. This may lead to development of AH and it's complications.

The significant role of NO in the pathogenesis of cardiovascular pathology raises a question of therapeutic usage of L-arginine as a substrate for its subsequent synthesis in the human organism. But, unfortunately, the most part of such experiments was carried out in vitro.

Several studies found that prescription of L-arginine (in daily dosage 2.1 g *per os*) allowed to decrease the level of diastolic blood pressure (DBP) in patients with AH [7, 8]. The researches explained this fact by normalization of endothelial regulation. In the following studies were obtained the results which demonstrated the effectiveness of antihypertensive treatment with simultaneous prescription of basic medicines and L-arginine [4, 5].

But other studies found that effectiveness of long-term prescription of this amino acid to hypertensive patients with comorbid pathology is comparable with placebo. The usage of L-arginine for the treatment of peripheral arterial insufficiency did not improve vascular function and relief the symptoms of intermittent claudication [6]. Similar results were obtained in the patients with acute myocardial infarction [9]. Low effectiveness of L-arginine in prevention of acute cardiovascular

pathology was found in several retrospective studies [8]. But at the same time other researches found that simultaneous prescription of L-arginine with isosorbide mononitrate or angiotensin II receptor blokers increases the effectiveness of antihypertensive and antianginal therapy [10]. That was explained by vasodilatation, decrease of systolic blood pressure (SBP) and lower myocardial oxygen consumption [10].

Thus, the practical aspects of L-arginine prescription in patients with AH remain controversial. For this reason, study of its pharmacodynamic effects is important.

Methods. A total of 80 adult patients (men and women in equivalent amounts) with AH gave their informed consent and were recruited for the study in Odessa national medical university (Ukraine). Patients were classified as having AH II stage according to Ukrainian and European criteria [13, 14].

Subjects with age less than 18 years, secondary AH, heart insufficiency, acute or chronic diseases, oncological pathology, pregnancy, breastfeeding or taking oral contraceptives were excluded. During the whole period of clinical observation, patients didn't change their usual diet and lifestyle. This excluded the changes in laboratory tests which were not caused by prescribed medicines.

Systolic (Korotkoff phase 1) and diastolic (Korotkoff phase 5) blood pressure (BP) was measured in the morning, in the supine position, triplicate at 10 min intervals with a mercury sphygmomanometer. The mean of the last two measurements was taken into consideration as BP (in mmHg).

Biochemical measurements were made in the blood samples. Blood was drawn after subjects had rested in the sitting position for 30 minutes. The blood components (glucose, total cholesterol (TH), high- (HDL) and low- density lipoproteins (LDL), triglycerides) were measured by standard methods.

The next clinical and laboratory examination was provided 30 days later.

The whole group of patients was divided into 2 subgroups according to the prescribed antihypertensive pharmacotherapy: 1^{st} subgroup (n=40) used Valsartan 0.08 g *per os* once a day in the morning + Amlodipinum 0.005 g *per os* once a day in the evening; 2^{nd} subgroup (n=40) in addition to the above mentioned medicines used L-arginine 1.0 g three times a day before meal.

For database management and statistical analyses was used Statistica software version 6.0 (Statsoft, Inc, Moscow, Russia), using an ά error less than 5% ($p<0.05$) for significance. All results are expressed as means (M) ± standard error of the mean (m).

Results. General characteristics of study participants are shown in Table 1.

Table 1

General Characteristics of Study Subjects

Variable	Men (n=40)	Women (n=40)
Age, y	53.2±9.7	56.3±6.7
Complaints, %:		
Anxiety	67.5	77.5
Headache	57.5	65.0
Loss of concentration	40.0	55.0
Insomnia	32.5	72.5
Dizziness	37.5	45.0
Fatigue	80.0	82.5
Mean SBP, mmHg	154.6±2.8	152.9±3.6
Mean DBP, mmHg	92.0±3.0	91.6±2.2
Mean HR, min	74.4±3.9	70.2±3.8
Glucose, mmol/l	5.2±0.5	5.4±0.5
TH, mmol/l	4.8±0.4	4.6±0.4
HDL cholesterol, mmol/l	1.36±0.2	1.32±0.2
LDL cholesterol, mmol/l	4.8±0.2	4.6±0.2
Triglycerides, mmol/l	1.4±0.2	1.2±0.2

Table 1 shows that in the research were mostly recruited middle-aged people (according to WHO classification).

Every patient had one or more of abovementioned complaints, which were more expressed in women. Most commonly the patients were disturbed with fatigue, which could not been caused by the severity of AH. The dynamics of the indicated neurological disorders in the both groups of comparison 30 days after the beginning of treatment is presented in Fig. 1.

In the process of treatment the psycho-emotional state of patients was significantly improved. Fig. 1 shows the decrease in the number of complaints, especially in the 2nd group. This can be explained as follows. One of the most common "stimulating" neurotransmitters in the brain is a glutamic acid. It activates a number of biochemical processes and lead to a significant increase in the concentration of NO due to sufficient income of exogenous L-arginine. Recent research found

that NO regulates the function of non-adrenergic, non-holinergic synapses. Thus, the above mentioned substance has neuroprotective effect, normalizes the higher nervous activity, improves learning ability and memory [11, 12]. Reduction of weakness under the influence of NO is associated with an increased synthesis of creatine in the striated muscle tissue. Important is the fact that one patient required lower dose of L-arginine (2.0 g/day) because of significant daytime sleepiness. After the correction of pharmacotherapy this complaint disappeared.

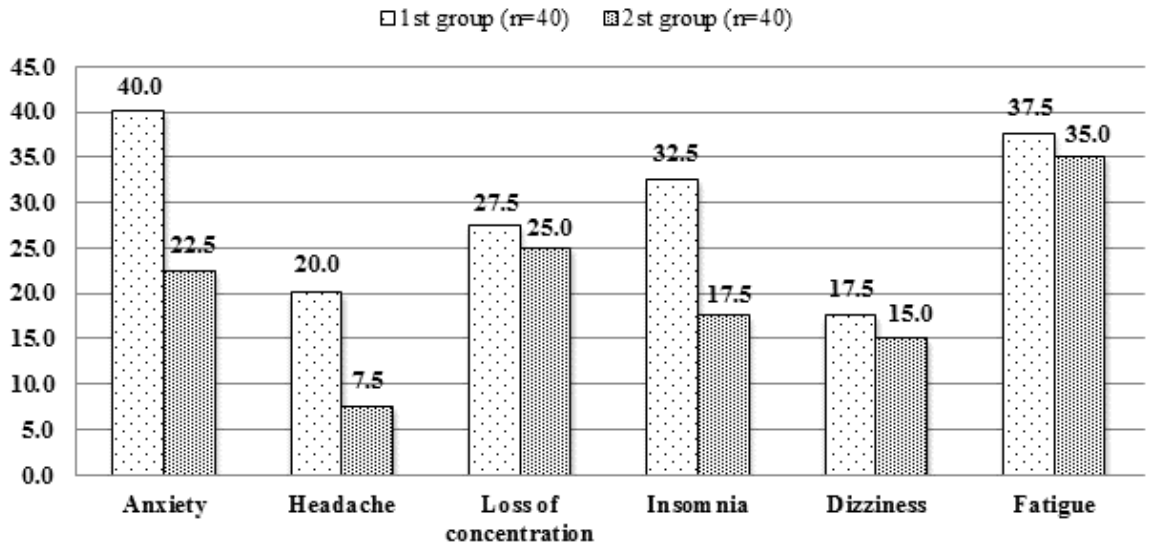

Fig.1. The dynamics of the main complaints in the both groups of comparison 30 days after the beginning of treatment (%)

In 5 patients the use of L-arginine before meal caused gastrointestinal disorders, such as nausea, flatulence and epigastric discomfort. That is why they began taking of this medicine during or after meal. Such change in the treatment didn't reduce the effectiveness of L-arginine.

Dynamics of SBP and DBP before and in 30 days of treatment is shown in Fig. 2 ($p<0.05$). Fig. 2 shows that before treatment both groups were comparable in mean levels of SBP and DBP. In 30 days the levels of SBP and DBP decreased, especially in the 2nd group of comparison ($p<0.05$). The effectiveness of antihypertensive therapy in the 1st group was 78%, the optimal levels of BP were achieved after 12-14 days of treatment. Patients of the 2nd group achieved stable levels of BP in 10-12 days, but in 10 patients the dose of Amlodipin was reduced to 0.0025 mg/day because of the threat of hypotension. Because of low compliance after 30 days of clinical trial 5 patients stopped taking prescribed medicines except L-arginine, but the level of BP remained normal. This fact confirms the important role of this amino acid in the pathogenesis of AH, but this hypothesis requires more thorough multidisciplinary research.

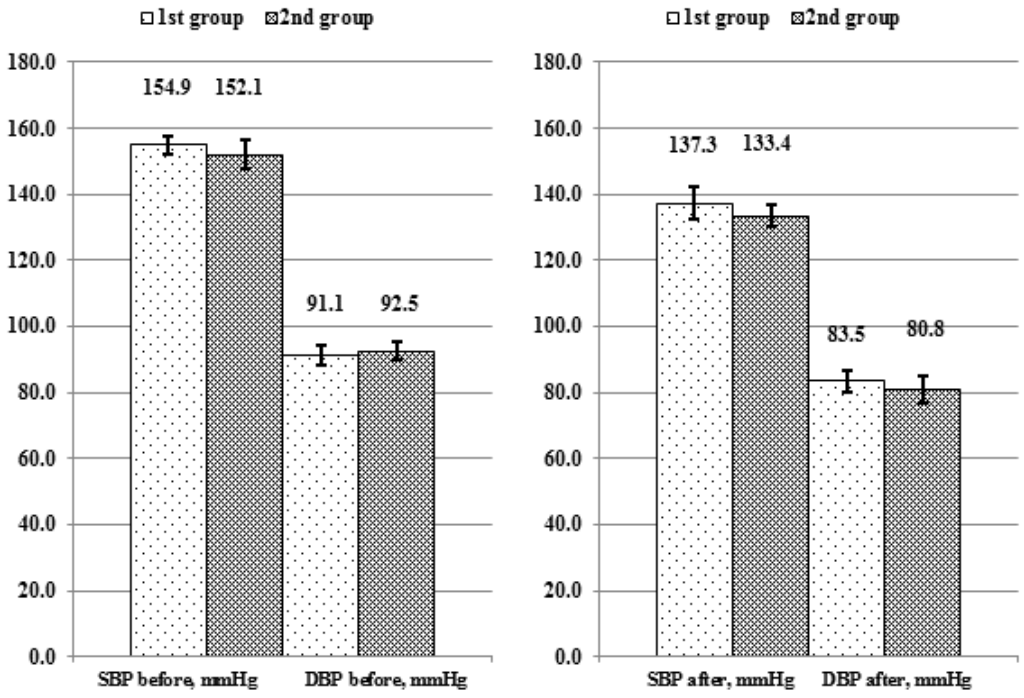

Fig. 2. Dynamics of SBP and DBP before and in 30 days of treatment

In this study were not found any effects of L-arginine on levels of glucose, total cholesterol, HDL, LDL and triglycerides (Fig. 3 and 4) ($p>0.05$).

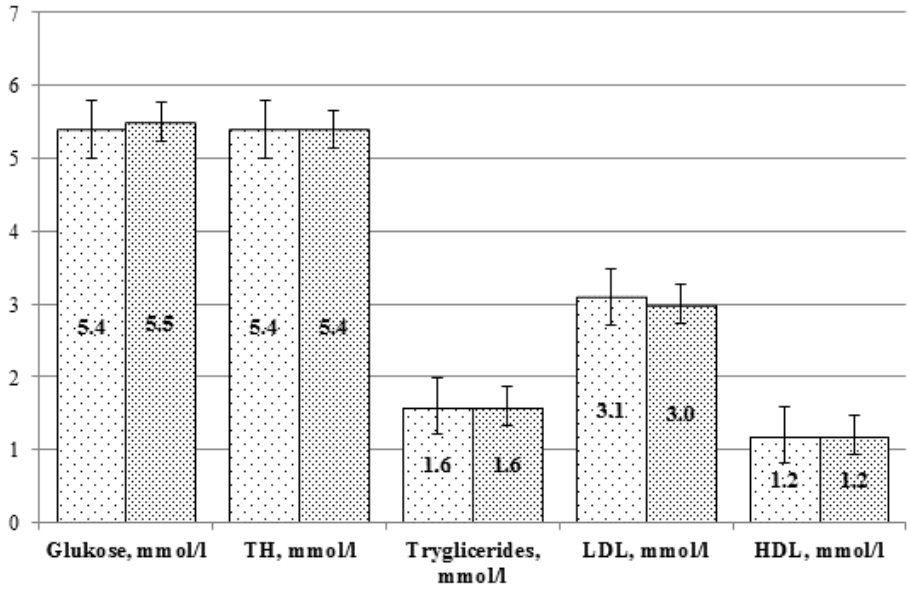

Fig. 3. Plasma levels of glucose, total cholesterol, HDL, LDL and triglycerides in the 1st group after 30 days of treatment

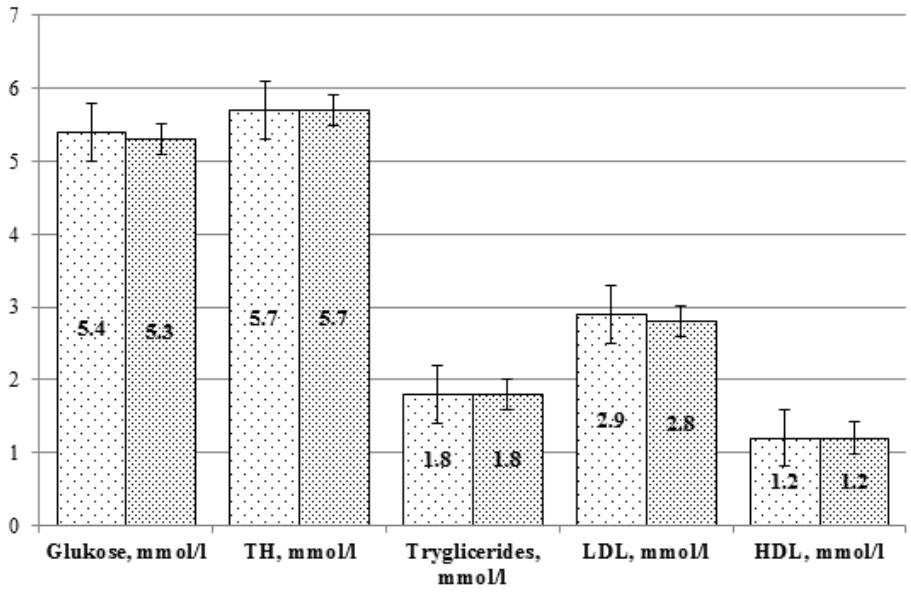

Fig. 4. Plasma levels of glucose, total cholesterol, HDL, LDL and triglycerides in the 2nd group after 30 days of treatment

This way, the addition of L-arginine to the complex pharmacotherapy of AH allows to improve its efficiency and reduce the doses of basic medicines. Absence of significant effect of L-arginine on the levels of blood glucose and lipids allows use it in patients with different risk factors or comorbid pathology.

Conclusions.

1. Addition of L-arginine to the basic antihypertensive medicines increases their efficacy and allows to achieve normal levels of BP in a shorter period of time.

2. L-arginine has positive psychotropic effects in patients with AH, but in some patients it can cause sleepiness.

3. No effects of L-arginine on lipids and blood glucose were found in this study.

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