L-Arginine in coronary heart disease: the research continues

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Atherosclerosis and coronary heart disease (CHD) are the chief causes of mortality in the developed countries. Almost entire adult population of these countries suffers from atherosclerosis. One of its most dangerous manifestations is CHD. According to current statistics, CHD-associated mortality is 48.5% of the overall cardiovascular mortality, occupying the first place [4]. Clinical and epidemiological studies that have been conducted in Ukraine indicate that the incidence of CHD over the past 20 years is stable at 12.4-13.1% and is steadily increasing with age. Already at the age of 30–39 years all forms of CHD can be found; in the age segment of 40–49 years, every 10th individual has signs of this disease, with the proportion increasing to every 4th individual over 50 years of age. A similar situation is observed with stable angina as one of the forms of CHD. The results of numerous studies demonstrate that the prevalence of angina also has a trend to increase with age: from 0.1–1% at the age of 45–54 years to 10–15% at the age of 65–75 years in females; from 2–5% at the age of 45–54 years to 10–20% at the age of 65-75 years in males [11, 17]. These data are consistent with the results of Framingham study, according to which the prevalence of CHD at the age of 55–62 years is 18% in males and 13% in females [2].

The main treatment objective in patients with chronic forms of CHD is improving quality of life by reducing the frequency of angina attacks, prevention of myocardial infarction and improving survival rates. The treatment of such patients is performed in accordance with the updated guidelines, which are based on the provisions of evidence-based medicine [10, 11]. Apart from lifestyle modifications, the program of treatment in patients with stable angina should include administration of beta-blockers (in poor tolerability of the latter or in contraindications calcium channel blockers should be used), acetylsalicylic acid 75 mg daily (in poor tolerability or in contraindications to the use of the latter, clopidogrel should be used instead of acetylsalicylic acid), statins (in elevated levels of total cholesterol) and prolonged release nitrates (in lack of overall therapeutic efficacy).

However, despite continuous improvement of therapeutic approaches and prevention in all forms of CHD, wide implementation of surgical treatments (angioplasty, stenting, coronary artery bypass grafting) and increasing efficiency of drug therapy, the treatment of angina remains a challenging task [4, 8].

Currently there is convincing evidence on the role of endothelial factors in development and progression of cardiovascular disease, including atherosclerosis, the latter being the foundation of CHD [1, 3, 6, 13, 15, 16, 23]. Thanks to intensive and diversified research, it became apparent that endothelium is a complex metabolic system and an actively functioning organ, which regulates vascular tone and other physiological processes [6]. The most important function of endothelium is regulation of vascular tone. Already in 1980, R.F. Furchgott and J.V. Zawadzki [19] found that acetylcholine-mediated relaxation of blood vessels occurs due to the release of endothelial relaxing factor (ERF). A true discovery in endothelium studies was determination of the chemical nature of ERF as nitric oxide (NO). It was established that most of the vasoregulating substances influence the vascular wall via a universal mechanism, endothelial synthesis of NO, the latter formed by the NO synthase enzyme from L-arginine. Nitric oxide activates guanylate cyclase in smooth muscle cells, which stimulates the synthesis of cyclic guanosine monophosphate (cGMP), which mediates vascular relaxation, as well as inhibits the activity of platelets and macrophages.

The vasoprotective functions of NO, besides participation in regulation of vascular tone, include release of vasoactive mediators and suppression of leukocyte adhesion to the vascular wall, which occurs by inhibiting the expression of adhesion molecules [25].

The mechanisms of anti-proliferative action of NO lie in its involvement in the remodelling of the vascular wall by suppression of mitogenesis and proliferation of sub-endothelial smooth muscle cells and fibroblasts [22]. In addition to that, NO inhibits the expression of pro-inflammatory genes of the vascular wall. It plays an important role in suppression of activation, adhesion and aggregation of platelets by increasing intra-platelet cGMP levels [24].

Thus, NO possesses a number of positive effects, which may become useful in the treatment of patients with chronic forms of CHD:

- vasodilation;
- reduction of cell proliferation;
- decreasing leukocytic activation and endothelial adhesion;

- decreasing platelet aggregation and adhesion to prevent thrombosis;
- inhibiting the synthesis of endothelin-1 (a potent endogenous vasoconstriction agent and a stimulator of proliferation and migration of myocytes in the vascular wall).

Arginine is one of the 20 amino acids of natural proteins; this amino acid is also a donor and natural carrier of nitrogen, thus supplying nitrogen to the system of NO-synthesising enzymes. The use of L-arginine, a precursor to NO, is theoretically substantiated for the therapy of a number of cardiovascular conditions. Arginine has several other pharmacological properties. In the late 90's of the last century, there were some publications, which described independent anti-anginal effect of arginine. As a result of multicentre studies, fundamental approaches to the therapy of refractory angina have been described. Currently, only L-arginine, testosterone and oestrogen are approved by Food and Drug Administration (FDA) for the treatment of refractory angina [14], which creates prospects for its application in patients with chronic forms of CHD and, above all, in patients with angina.

Currently, L-arginine is used as a therapeutic agent in diseases, which predominantly affect blood vessels. Thus, the Department of Atherosclerosis and Chronic CHD of the National Research Centre 'Institute for Cardiology named after Academician N.D. Strazhesko' associated with the Academy of Medical Sciences of Ukraine has conducted an 8-week clinical study of oral L-arginine at a dose of 6 g/day. This study has demonstrated substantial improvements of quality of life in the patients receiving the drug, including reduced nitroglycerin requirements; many patients reported cessation of angina decubitus [9, 14]. M.F. Zinkovskiy [5] is considering L-arginine in pulmonary arterial hypertension for the treatment and prevention of pulmonary hypertensive crises.

The Department of Internal Medicine No. 2 of the National Medical University named after A.A. Bogomolets has conducted a study aimed at evaluating the efficacy of L-arginine as a constituent of multimodality therapy in patients with stable angina and post-infarction cardiosclerosis.

This randomized open clinical study under a limited program was performed in accordance with the requirements of the State Pharmacological Centre of the Ministry of Health of Ukraine to limited clinical trials (the Order of the Ministry of Health of Ukraine No.66 dated 13.02.2006, the Order of the Ministry of Health of Ukraine No. 245 dated 17.05.2007).

The inclusion criterion was the presence of stable effort angina, functional class (FC) I–III in accordance with existing guidelines [12]. The diagnosis of CHD was based on the results of the graduated exercise test and the history of prior (at least 6 months ago) myocardial infarction or surgical revascularization. The patients with non-coronary myocardial problems, diabetes mellitus Type 1, symptomatic hypertension, congestive heart failure of NYHA FC above III, unstable angina or FC IV angina, as well as subjects with severe non-cardiac comorbidities were excluded from the study.

A total of 60 patients with FC I–III stable effort angina were assessed; all patients had been hospitalized to the Clinic of Cardiology of Alexandrovskaya Hospital of the City of Kiev between November 1, 2009 and May 31, 2010.

All patients received conventional therapy (the drugs and doses were not changed throughout the entire period of observation), which included acetylsalicylic acid (75-150 mg per day), bisoprolol (2.5-10 mg per day) and simvastatin (20-40 mg per day) [18, 20]. Whenever concomitant hypertension was present, the therapeutic schedule was appended with enalapril (10-40 mg per day to achieve the target values of office BP <140/90 mm Hg). [20]. Study subjects were allowed to use short-acting sublingual nitroglycerin as required.

No sooner than 3 weeks after initiation of the above drugs (provided the patient's condition was stable and target BP was consistently maintained) informed consent to participate in the study was obtained from the patients. The patients were consequently enrolled and randomised into two groups 30 subjects each. The patients of the main group (n=30) received additional arginine hydrochloride (Tivortin®, by 'Yuria-Pharm', Ukraine), supplied as 4.2% intravenous solution at the dose 100 mL once a day (6–10 days) with subsequent transition to oral solution 5–10 mL 3 times a day for 4 weeks. The patients of the control group (n=30) continued to receive their previously initiated therapy.

Table 1. Clinical characteristics of study subjects (M±m)

The parameter	Main group (n=30)	Control group (n=30)
Age, years	58.4±2.3	59.5±2.1
Gender: male	22 (73.3)	23 (76.7)
female	8 (26.7)	7 (23.3)
Age (males), years	58.8±2.2	60.1 ±2.3
Age (females), years	57.3±2.2	58.0±2.3
Smoking	12 (40.0%)	14 (46.7%)
Hypertension	19 (63.3%)	20 (66.7%)
Body mass index>30	14 (46.7%)	15 (50.0%)
Type 2 diabetes	9 (30.0%)	11 (36.7%)

Both groups were comparable in terms of age, gender and the frequency of the main risk factors (see Table 1). The significance of differences between the investigated indices in all groups was >0.05.

Screening assessments included history, physical assessment, complete blood count, biochemical tests of renal and hepatic function and measurement of office blood pressure (BP). The bicycle ergometry test in order to verify CHD and determine exercise tolerance was performed using the hardware/software complex Schiller PC-104 with the bicycle ergometry unit Schiller Ergosa-

Table 2. HR and office SBP/DBP in patients of the two groups in course of treatment (M±m)

The parameter	Main group (n=30)			Control group (n=30)		
	Pre-treatment	After treatment	P	Pre-treatment	After treatment	P
HR, bpm	63.2±2.6	62.8±2.3	>0.05	61.6±2.4	60.9±2.2	>0.05
SBP (mmHg)	132.1 ±2.4	130.3±2.7	>0.05	131.6±2.5	132.0±2.6	>0.05
DBP (mmHg)	81.2±1.8	82.5±1.8	>0.05	83.1 ±1.9	82.4±1.7	>0.05

Table 3. The findings of bicycle ergometry test in study subjects of the two groups in course of treatment (M±m)

The parameter	Main group (n=30)			Control group (n=30)		
	Pre-treatment	After treatment	P	Pre-treatment	After treatment	P
Threshold challenge, W	78.6±2.7	93.3±2.9	<0.05	80.2±2.4	81.3±2.6*	>0.05
Challenge time, min	6.92±0.41	8.57±0.45	<0.05	6.81 ±0.38	7.22±0.42	>0.05
Ischaemic EKG changes	19 (63.3%)	19 (63.3%)	>0.05	21 (70.0%)	21 (70.0%)	>0.05

*p<0.05 compared to the respective values in the patients treated with arginine hydrochloride.

na 911 (Switzerland). A symptom-limited protocol was applied, assuming the baseline load of 50 W with 25 W increment every 3 minutes.

Assessments of exercise tolerance and measurements of office BP were performed before administration of the investigational product and on Day 45–50 of treatment [21].

Analysis of the material obtained was performed using the clinically accepted methods of variation statistics, the Wilcoxon test (for related sets) and Mann-Whitney test (for unrelated sets). The changes were considered significant if the p value of probability was less than 5% (p <0.05), the latter being universally accepted as sufficient in biomedical research [7].

Prior to treatment, the patients of both groups complained of angina attacks consistent with FC II–III: 18 patients (60% of subjects) in control group and 17 patients (56% of subjects) in the main group. Dyspnoea on exertion was noted by 16 and 15 patients, respectively. No patients had oedema. The signs of heart failure were consistent with FC I–II in both groups. No significant changes in the frequencies of clinical indices have occurred after treatment: one patient of the control group noted less frequent attacks of angina and reduced nitroglycerin requirements (from 3 tablets per day to just one); 5 subjects have noticed improved exercise tolerance (increased walking rate and the total walking time during the day). Among the patients of the main group, 3 patients have noticed decreased frequency of anginal attacks and reduced nitroglycerin intake (a reduction by 1–2 tablets per day). Improved exercise tolerance was noted by 7 patients in this group (manifested as covering longer distance prior to the need to take nitroglycerin). However, the analysis has demonstrated that the differences in the frequency of the indices before and after treatment were not confirmed across the groups (p<0.05 in all cases).

Prior to treatment, heart rate (HR) and systolic/diastolic BP (SBP/DBP) were not significantly different across the groups (see Table 2; p > 0.05; in all cases concerning the difference between the indices in the groups compared). The therapy conducted failed to produce any substantial influence upon the values of these indices, p>0.05 (in all cases in the groups before and after treatment).

The results of the bicycle ergometry challenge test have shown that treatment with Tivortin® contributed to a significant increase in exercise tolerance (by 18.7%, p<0.05), which was not observed in the control group (see Table 3). Similar results were obtained in analysis of exercise time, viewed as a more sensitive indicator (increase by 23.8%, p<0.05). In the meantime, there were no significant changes of challenge time in the control group in course of treatment (inter-parameter p value before and after treatment >0.05).

During Tivortin® therapy, there were no changes concerning the numbers of such patients, which had to stop the exercise due to emergence of ischaemic ECG patterns. This can be explained by the presence of pronounced changes of coronary vessels in this group of patients, which does not allow eliminating the symptoms of ischaemia, especially given the short period of observation and previously initiated adequate anti-anginal therapy.

In this situation, increased exercise tolerance can be viewed as a success, since it improves the quality of life.

The treatment with Tivortin® was well tolerated. Throughout the entire course of treatment, there were no cases of such adverse events, which would require discontinuing the drug. Seven patients (23.3% of the patients in the main group) experienced transient heat sensation during infusion of the drug, which reversed when the infusion rate was reduced. The patients of both groups reported improved overall condition.

CONCLUSIONS

Inclusion of Tivortin® into the standard therapy of patients with stable angina of functional class I–III increases the exercise tolerance according to the findings of the bicycle ergometry test by 18.7% and the time of exercise by 23.8%.

In the setting of stable angina and post-infarction cardiosclerosis (without manifesting heart failure), inclusion of Tivortin® into the multi-modality treatment program is well tolerated by the patients and does not affect BP and HR levels.

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