The Clinical Role of Nitric Oxide and L-arginine in Asthma

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Abstract

NO is an important biological marker in the activity of the inflammatory process and endothelial dysfunction in bronchopulmonary diseases. Endothelial dysfunction appears as a primary element for vessel wall lesion that causes formation of the cardiovascular effects in asthma.

Cardiovascular effects are considered as system displays of various diseases, among which endothelial dysfunction appears as the primary element of a vessel wall lesion. Studying NO metabolites and L-arginine content plays an important role for required correction in the respiratory system endothelium.

Keywords: nitric oxide; L–arginine; asthma; endothelial dysfunction.

State of the Problem

The role of NO, which is one of the major mediators of the functioning of various bodies and systems, has been actively studied in pulmonary diseases during the last years [1,2,3].

It has been established that the cytoprotective effect of NO is based on inhibiting proliferation of smooth muscle cells, preventing monocyte cell chemotaxis, and suppressing the adhesion of leukocytes to endothelial cells [4]. Inhibition of NO synthesis leads to vasoconstriction, which raises the risk of arterial hypertension development, cell membrane damage by free-radicals, atherosclerosis development, and a decrease of anti-tumor and anti-infective activity of the immune system. NO has been found to have a positive impact on the destructive action of stress reactions. This impact is caused by direct reduction of the stress-activated oxidation of free radicals due to an increase in activity of antioxidant enzymes [5]. Additionally, NO possesses independent antioxidant properties. Lack of NO causes a spasm of smooth muscles of the bronchial tubes and mediates bronchospasm development, and there are data that show a decrease in synthesis of NO in bronchial asthma and chronic obstructive bronchitis [6,7].

As a multifunctional factor [8-10], NO causes myorelaxation, vasodilatation and anti-proliferative effects, possesses free-radical properties, and rheology stabilizing properties [11-14]. Promoting the activity of Th-2 cells and inhibiting the activity of Th-1 cells, NO powerfully impacts immune system function. NO is the factor of chemotaxis of eosinophils and neutrophils; it inhibits their apoptosis and stimulates atopic reply [15,16].

L-Arginine is a conditionally nonessential amino acid, which was allocated in 1886 by E. Schulze and E. Steiger. In 1897, E. Schulze established its structure. The average daily consumption of L-arginine must be 5.4 g. The needs of tissues and bodies for arginine are satisfied with autogenous synthesis and/or with food, but in the conditions of stress or illness, this amino acid becomes essential. Arginine is the precursor for synthesis of ornithine, proline, polyamine, creatine, and agmatine. However, the leading role of arginine in a human body is to be a substratum for NO synthesis [17,19].

The typical diet gives 3–6 g of L-arginine per day. The basic sources of L- arginine are seeds of various plants, wheat germ, oats, beans (a soya, peas, a string bean), meat (duck, goose, ram), nuts (walnut, coconut, a filbert, pistachios, a peanut), fish, gelatin, dairy and seafood, with a bioavailability
by approximately 60%. According to M. Walser (1983), a 70 kg adult, using 50 g of protein per day, spends 0.2 mmol (34.8 mg) L-arginine per 1 kg of body weight, or only 2.4 g of L-arginine per day.

At the present time, there is sufficient clinical experience of the application of L-arginine in various areas of medicine. In the Ukrainian Research Center of Cardiology named after ND Strazhesko, V.A.Slobodsky [19] studied the effects of L-arginine aspartate solution (Tivortin aspartate) for per-oral administration in 38 outpatients with coronary disease having a stable angina pectoris of II-IIIIFK. The preparation was applied in a dose of 15 ml (1.71g) twice a day for 2 months in addition to standard therapy. Results reflected improvement of endothelium function, increasing tolerance for physical activity, and improvement of patient quality of life. The drug significantly improved endothelium-dependent vasodilatation (EDV) from 3.35±0.48 to 6.24±0.41 (p<0.01). In tests with the prescribed physical activity, the time prior to the electrocardiographic evidence of ischemia development and/or pain occurrence from 7.18±0.64 to 9.62±0.61 minutes (p<0.05) significantly increased. Furthermore, a statistically significant increase of 34% (p<0.05) in total performed work was noted. Nitroglycerin application decreased from 3.61±0.5 to 1.1±0.24 tablets per day (p<0.01).

N. Nagaya et al. [20] found positive effects of L-arginine on hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension, who were administered per-oral doses of L-arginine (0.5g/10 kg of body weight, 3 times per day) in a randomized, double-blind, placebo-controllable study with 19 participants. The results of this study showed a substantial increase in serum L-citrulline concentration, which was associated with an increase in NO production; a decrease of average pulmonary arterial pressure by 9% (from 53±4 to 48±4 mmHg; p<0.05) and resistance of pulmonary vessels by 16% (from 14.8±1.5 to 12.4±1.4 Wood’s Unit; p<0.05); and a moderate decrease in system arterial tension (from 92±4 to 87±3 mmHg; p<0.05). Administration of L-arginine within 1 week led to a slight increase in the maximum consumption of oxygen (from 831±88 to 896±92 ml/minutes; p<0.05) and a significant reduction in the slope of the minute ventilation/ carbon dioxide production curve (VE/VCO2 slope) (from 43±4 to 37±3; p<0.05) [11].

A. Jabłecka and co-authors (2004) found an essential increase in the level of NO and the general antioxidant status (total antioxidant status - TASS) in connection with administration L-arginine within 28 days in a dose of 2-4 g three times a day in 32 patients with atherosclerotic lesion of peripheral arteries (II and III stages on Fontaine).

In pilot study by R.K. Oka and co-authors [21], patients were randomly assigned to oral doses of 0, 3, 6 or 9 g of L-arginine daily in three divided doses for 12 weeks. Treadmill testing was performed prior to administration of the study drug and again after 12 weeks of treatment. The study drug was well tolerated, with no significant adverse effects of L-arginine therapy. There was no significant difference observed in absolute claudication distance between the groups. However, a trend was observed for a greater increase in walking distance in the group treated with 3 g L-arginine daily, and there was a trend for an improvement in walking speed in patients treated with L-arginine. This pilot study provided data for safety, for power calculation and for dosing for the larger definitive trial that is now underway.

Some studies have shown that L-arginine application in mice led to an increase in eNOS-mediated NO production and a decrease in the expressiveness of the atherosclerotic process [22,23].

At the same time, several studies have shown that administration of L-arginine to healthy patients of advanced age did not have a considerable influence on initial data [14,16]. Results of the meta-analysis confirm that the effect of L-arginine depends on the initial status of the endothelium. Application of L-arginine is not able to increase the EDV in healthy individuals with normal function of the endothelium, at the same time the preparation may be effective for endothelial dysfunction. It has also been found that short-term L-arginine application improves endothelium function [10].

A.M. Wilson and co-authors (2007) have shown that long-term L-arginine administration may have an adverse effect: L-arginine in a dose of 3 g/day for 6 months reduced the availability of NO (concentration of NO in blood plasma and urine and concentration of citrulline in blood plasma was estimated). Long-term L-arginine application has been found to reduce the sensitivity of smooth muscle cells to NO in response to a pressure shift [16]. In long-term L-arginine application, a probable tolerance to nitrates develops, which has also been observed in long-term application of exogenous NO donator - nitroglycerin. A.M. Wilson believes that a transient increase in NO level caused by L-arginine may inhibit activity of NOS through nitrosylation of this enzyme or transporter of L-arginine.

At the same time, another study showed that intravenous L-arginine (30 g during 30 minutes), in comparison with a placebo, led to a significant decrease in arterial pressure and an increase in heart rate [24]. The effect on diastolic BP, in comparison with systolic BP, was more pronounced; it was connected with a decrease in peripheral arterial resistance in accordance with Doppler femoral artery data. These hemodynamic effects were not observed against a placebo. After the introduction of L-arginine, cGMF excretion was raised by 65.4%, and only by 25.1% after placebo application; urine NO3 excretion was raised by 79.7% after introduction of L-arginine. The plasma concentration of L-arginine was raised approximately 10 times after drug infusion and cGMF excretion with urine was increased by the same amount.

The listed positive results, and many other studies, were the basis for our study on evaluating the impact of L-arginine on the clinical course of asthma and the functional status of the endothelial system with this disease.

We studied 82 patients aged from 18 to 55 (38.5±4.2 years) with mild and persistent-moderate asthma with a duration of more than 12 years (16±4.5 years). After giving informed consent, the patients were divided into two groups. The patients in the study group (n=42) were subjected to the standard treatment (GINA, 2007) and, in addition, L-arginine administration. L-arginine (Tivortin, URIA-PHARM, Ukraine) was administered daily by intravenous infusion in
a dose of 4.2 g for 30 min for 10 days. The patients of the
comparison group received the standard treatment only. The
control group included 20 healthy volunteers. The condition of
the endothelial systems was estimated before and after the 10-
day course of treatment using following parameters: changes
in the level of the main stable NO metabolites (NO2 and
NO3), which were identified by a Griss reagent (P.P. Golikov
et al., 2004) in blood plasma and the exhaled air condensate.
The exhaled air condensate gathering was done according to
G.I. Sidorenko’s method, modified by us. The definition of
the L-arginine level in plasma was carried out by thin-layer
chromatography. Results were statistically processed using
the computer software package Microsoft Excel (“Packet
Analysis”). Quantitative and serial parameters are presented
as the mean (M) ± standard deviation (SD), quality - as the
absolute number of observations and proportion (in %) of
the total number of patients for the sample as a whole or
relevant group. A probability value of \( P<0.05 \) was considered
statistically significant.

Initial data showed that the content of stable NO
metabolites in blood and the exhaled air condensate was lower
than control indicators; the L-arginine level in plasma was
also significantly lower in both groups of patients. After the
10-day treatment course, indicators of endothelial function
were changed. In the study group patients, L-arginine level
significantly rose (\( p<0.01 \)) and almost reached a norm; the
level of NO metabolites in the blood and the exhaled air
condensate also significantly increased (\( p<0.01 \)) but did not
reach a norm. In the comparison group patients, changes in
initial indicators were small and statistically insignificant.

In sum, studies of the last years testify a wide spectrum
of bioregulator effects of nitrogen oxides system, which is
unique mediator of intercellular interaction. NO is an important
biological marker in the activity of the inflammatory process
and endothelial dysfunction in bronchopulmonary diseases.
Endothelial dysfunction appears as a primary element for vessel
wall lesion that causes formation of the cardiovascular effects
in asthma. Studying NO metabolites and L-arginine content
plays an important role for required correction in the respiratory
system endothelium. Our research shows that a long duration
(average 16±4.5 years) of mild and persistent-moderate asthma
results in an endothelial dysfunction with a decrease in plasma
L-arginine level, concentration of NO metabolites in blood and
EAC. L-arginine administration against the background of
pathogenetic therapy improves the endothelial function.

**Competing interests**

The authors declare that they have no competing interests.

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