L-arginine from the viewpoint of evidence-based medicine

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Amino acid L-arginine is a substrate for nitric oxide synthesis.

Arginine is a conditionally essential amino acid, first isolated in 1886 by E. Schulze and E. Steiger; its structure was determined by E. Schulze and E. Winterstein in 1897. The average daily consumption of L-arginine is 5.4 g. The physiological requirements of tissues and organs in most mammals of arginine are met by its endogenous synthesis and/or dietary intake; however, in the young and in adults in stress or disease this amino acid becomes essential. Arginine is an important precursor for the synthesis of proteins and many biologically active molecules, such as ornithine, proline, polyamines, creatine and agmatine However, the main function of arginine in human body is to be a substrate for the synthesis of nitric oxide (NO) (Visek W.J., 1986; Wu G., Morris S.M. Jr., 1998; Böger R.H., 2007).

Dietary L-arginine is absorbed in the small intestine with subsequent transport to the liver, where most of it is utilised in the ornithine cycle. The fraction of L-arginine not metabolised in the liver is used as a substrate for NO production. The main source of endogenous arginine in the body is protein metabolism; however, the endogenous synthesis of arginine does not play an important role in the regulation of homoeostasis in healthy adults (Wu G., Morris S.M. Jr., 1998; Böger R.H., 2007).

Under physiological conditions, the synthesis of NO from L-arginine occurs with the NO-synthase enzymes (NO-synthase — NOS), L-citrulline being the second product of the reaction. NOS is the only currently known enzyme to execute the above process with 5 cofactors / prosthetic groups simultaneously (flavin adenine dinucleotide, flavin mononucleotide, heme, tetrahydrobiopterin and calcium / calmodulin), being, therefore, one of the most regulated enzymes in the nature (Bryan N.S. et al., 2009).

There are several isoforms of NOS, named for the type of cells, wherein they were first isolated: neuronal (nNOS, NOS I), endothelial (eNOS, NOS III) and macrophagal (iNOS, NOS II). Both eNOS and nNOS are constantly present in the relevant cells, that is, their expression is constitutional.

In the cardiovascular system, eNOS is mainly produced in the endothelial cells, its production being supported by biochemical stimuli such as acetylcholine and bradykinin, as well as by stimulation of mechanoreceptors by shear stress1. ENOS activity directly correlates with the concentration of intracellular calcium. eNOS plays a leading role in the maintenance of constant baseline levels of NO, which is associated with implementation of local endothelial cytoprotection and maintenance of vascular homoeostasis, and with physiological regulation of blood pressure (BP). In addition, eNOS was also found in other cells and tissues, such as

cardiomyocytes, erythrocytes, megakaryocytes and platelets (Gurevich M.A., Sturov N.V., 2006; Böger R.H., 2007; Gkaliagkousi E. et al., 2007).

Within the vascular network, iNOS is present not only in macrophages, but also in lymphocytes, endothelial cells, smooth muscle cells or fibroblasts, being activated under the influence of bacterial endotoxins and inflammatory cytokines (such as tumour necrosis factor-alpha and interleukin). The activation of iNOS is calcium-independent, causing NO synthesis at high concentrations (up to 1000 times higher compared to eNOS). In turn, nNOS synthesises physiological amounts of NO mainly as a transmitter in the brain and in the peripheral nervous system, for example, in the non-adrenergic non-cholinergic autonomic nerve fibres. Currently there is evidence of constitutive iNOS expression in certain tissues, as well as the evidence of inducible forms of eNOS and nNOS (Böger R.H., 2007; Bryan N.S. et al., 2009; Lubos E. et al., 2009).

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[1] Shear stress is the force of blood flow, which is directed tangentially to the endothelial surface of the blood vessel (Paszkowiak J.J., Dardik A., 2003).

The physiological role of nitric oxide

NO plays an important role in mammalian physiology, possessing an extensive range of bioregulatory effects. The NO molecule is one of the smallest molecules among the known biological messengers. Due to its chemical simplicity, the effects of NO may be regulated exclusively by its concentration and stability. The NO molecule penetrates cell membranes easily, without the need for either channels or receptors. The NO-induced signal period is quite short, since NO is rapidly oxidized to nitrates into nitrites. That is precisely why the biological effects of NO are limited to its place of origin. In most cases, NO targets the heme portion of soluble guanylate cyclase. The NO catalyses the formation of cyclic guanosine monophosphate (cGMP), which is the very substance to determine most of the physiological effects of NO. However, NO is currently known to possess other physiological effects, independent of guanylate cyclase activation or even NOS, including posttranslational modification of proteins, lipids and other biomolecules. Other possible targets of NO are the soluble adenosine diphosphate (ADP)-ribosylating enzymes and transcription factors, through which NO may directly influence gene transcription and translation of mRNA (Buhimschi I.A. et al., 1998; Markov Kh.M., 2000; Bryan N.S. et al., 2009).

The specific types of NO targets depend on the environment and the amounts of NO produced. Local NO levels are determined by the intensity of its synthesis or exogenous formation and the intensity of inactivation. The physiological action of NO varies from modulating vascular system to regulating immune processes (cell-mediated immunity, the action of neutrophilic granulocytes against pathogens and non-specific immune responses) and the control of neural functions (signal transmission in non-adrenergic non-cholinergic neurons, synaptic plasticity in the central nervous system, oscillatory activity of neuronal networks and neuroprotection) (Stepanov Yu.M. et al., 2004; Böger R.H., 2007; Lubos E. et al., 2009) (Table).

Table **The roles of NO in the functioning of various bodily systems (Stepanov Yu.M. et al., 2004)**	
Functional systems of the body	**Physiological responses**
The cardiovascular system	Relaxation of blood vessels in the brain, retina of the eye, heart, lungs, kidneys, intestines, cavernous tissue and the cardiac muscle.
Respiratory system; digestive tract and urogenital tract	Relaxation of smooth muscles in the trachea, stomach, intestines, urinary bladder and uterus
Central and peripheral nervous systems	The neuro-modulating activity which determines long-term potentiating effects, memory formation, pain perception and visual analysis
The endocrine system	The regulation of synthesis and secretion of hormones: insulin, prolactin, thyroid hormone, parathyroid hormone, adrenal hormones and the hormones of the reproductive cycle
The system of haemostasis	Regulation of interactions of leukocytes with vascular wall. Regulation of platelet activity
The immune system	Counter-pathogenic reactions, non-specific cytotoxicity, anti-tumour protection, the pathogenesis of toxaemia and transplant rejection

The role of NO in the maintenance of vascular homoeostasis can be summarised as regulation of vascular tone, proliferation and apoptosis, as well as regulation of oxidant processes. Furthermore, angioprotecting properties are inherent to NO (Gurevich M.A., Sturov N.V., 2006; Elskyi V.N. et al., 2008). NO is also responsible for the anti-inflammatory effects, such as inhibiting the expression of intercellular adhesion molecules-1 (ICAM-1), vascular cellular adhesion molecules-1 (VCAM-1) and the tissue factor and inhibiting the release of chemokines, such as monocyte chemoattractant protein-1 (MCP-1). In addition, NO inhibits platelet aggregation and has a fibrinolytic effect (Chatterjee A., Catravas J.D., 2008).

Nitric oxide is a powerful peripheral vasodilator

Discovery of the role of NO as a cardiovascular signal molecule earned R. Furchgott, L. Ignarro and F. Murad the Nobel Prize in Medicine and Physiology in 1998 (Bryan N.S. et al., 2009).

After formation in the vascular endothelium, NO is bound with trivalent iron in the heme of the cytochromes of C-oxidase in the mitochondria, thus regulating certain transcription factors, such as hypoxia-inducible factor-1 (HIF-1); alternatively, NO diffuses rapidly into the blood. In the vascular lumen NO is rapidly absorbed by erythrocytes, entering into a reaction with divalent iron of the heme part of oxyhaemoglobin, thus forming methaemoglobin and NO3-. NO also diffuses into the cells of vascular smooth muscles, adjacent to the endothelium, where it modulates the activity of heme-containing guanylate cyclase. This enzyme dephosphorylates guanosine to produce cGMP, which in turn activates K + channels and inhibits the entry of calcium ions into smooth muscle cells via direct inhibition of calcium channels, also activating the protein kinase which phosphorylates the light chains of myosin and the proteins of sarcoplasmic reticulum, thus promoting the sequestration of calcium ions into the sarcoplasmic reticulum. As a result, smooth muscles relax, therefore adjusting the vascular lumen to tissue demands; this process is referred to as endothelium-dependent vasodilation (EDVD). The donator-released NO acts in the very manner as the endogenously produced substance. The ability of vascular smooth muscle cells to utilize

exogenous NO is referred to as endothelium-independent vasodilation (Gornik H.L., Creager M.A., 2004; Lubos E. et al., 2009).

Although the intracellular concentration of L-arginine is substantially higher than in plasma or extracellular fluid, endothelial cells were demonstrated to be able to capture extracellular L-arginine rapidly to synthesise NO (Böger R.H., 2007). In low plasma concentrations L-arginine selectively improves endothelial function; in medium concentrations it may exert direct vasodilating action due to stimulation of insulin and somatotropin secretion; the high levels of L-arginine cause non-specific vasodilation (Yi J. et al., 2009)

Nitric oxide deficiency as a key element of endothelial dysfunction

According to modern concepts, the endothelium is not just a semi-permeable membrane lining of the inner surface of the heart and blood vessels, but rather n active endocrine organ diffusely present in all tissues; it appears to be the largest endocrine organ in the body (the body of an average weight adult contains approximately a trillion of active endotheliocytes, weighing a total of 1,8 kg), capable of continuous production of biologically active substances. One of the main functions of the endothelium is a balanced production of regulatory substances, which determine the integral work of the circulatory system. These substances play an important role in the body, being responsible for the regulation of vascular tone (secretion of vasoactive mediators), maintenance of their anatomy (the synthesis and the inhibition of proliferation factors), maintaining haemostasis (the synthesis and the inhibition of the factors responsible for fibrinolysis and platelet aggregation); also, they participate in local inflammation (production of pro- and counter-inflammation factors). The following are the main factors to activate endothelial cells: the mechanical impacts of blood flow and the stress of the vascular wall; platelet factors (serotonin, ADP, thrombin); circulating and/or intramural neurohormones (catecholamines, vasopressin, acetylcholine, endothelin, bradykinin, angiotensin II, adenosine, histamine) and hypoxia. Under normal conditions, endothelium responds to stimulation by augmented synthesis of the substances, which relax smooth muscle cells of the vascular wall. The normally functioning endothelium is characterised by balanced formation of vasoconstrictors (endothelin-1, thromboxane A2, prostaglandin H2) and vasodilators (NO, endothelial hyperpolarization factor, prostacyclin, C-type natriuretic peptide, etc.) (Belousov Yu.B., Namsaraev Zh.N., 2004; Gornik H.L., Creager M.A., 2004; Golovchenko Yu.I., Treshinskaya M.A., 2008; Elskyi V.N. et al., 2008).

The greatest vasodilating effect is peculiar to NO. As an endothelial relaxation factor, NO was discovered in 1980; R.F. Furchgott and J.V. Zavadzki have demonstrated that the action of most substances which influence the vascular tone is mediated by the release of NO from the endothelium. NO is present in all endothelial cells regardless of the size and functions of the vessels. In a normally functioning endothelium, low levels of NO are continuously released to keep blood vessels dilated and provide for non-adhesion of blood corpuscles to the endothelium. When exposed to various damaging factors (mechanical, infectious, metabolic, related to immune complexes, etc), endothelial cells diminish their ability to release relaxing factors, whereas the formation of vasoconstricting factors is either intact or increased; this condition is defined as endothelial dysfunction (ED) (Belousov Yu.B., Namsaraev Zh.N., 2004; Gornik H.L., Creager M.A., 2004; Golovchenko Yu.I., Treshinskaya M.A., 2008; Elskyi V.N. et al., 2008).

A key factor in the development and progression of vascular disease is the regulation of NOS and the bioavailability of its substrates and cofactors (Chatterjee A., Catravas J.D., 2008). Local availability of L-arginine as a NOS substrate may be reduced due to the activity of arginase, which utilises L-arginine to produce urea and ornithine, thus competing with NOS for the availability of substrate. Various studies indicate that induction or activation of arginase I or arginase II lead to impaired NO production and, as a result, to ED. The endogenous NOS inhibitor, asymmetric dimethylarginine (ADMA) also inhibits NO formation when accumulated in various disease. A

correlation was found to exist between increased ADMA levels and cardiovascular disease (CVD). Increased ADMA levels are found in patients with hypercholesterolemia, hypertriglyceridemia, insulin resistance, Type 2 diabetes mellitus (DM), renal failure and cardiac syndrome X (Gornik H.L., Creager M.A., 2004; Böger R.H., 2007).

The pathogenetic role of nitric oxide deficiency

Impaired synthesis or function of NO within the vascular system is an important pathogenetic factor of such diseases as arterial hypertension (AH), atherosclerosis and diabetic angiopathy (Böger R.H., 2007). The following complications may also occur due to lack of this chemical: acute myocardial infarction (MI), unstable angina, atherothrombosis, thrombotic microangiopathy, thromboembolic cerebrovascular disease and preeclampsia (Gurevich M.A., Sturov N.V., 2006).

Currently ED is viewed as the main mechanism behind AH. Impairment of NO-dependent relaxation of arteries in patients with AH can be attributable to several mechanisms: decreased NO production, accelerated No breakdown and changed cytoarchitectonics of the vessels. Intracellular oxidative stress is considered to the most important factor to decrease EDVD, since free radical oxidation dramatically reduces endothelial production of NO. The high risk of cerebral complications in patients with AH is considered to be related specifically to the development of ED, which prevents adequate regulation of cerebral blood flow. Impaired autoregulation of cerebral perfusion is a predictor of encephalopathy and transient ischaemic attacks (TIAs) (Vizir B.A., Berezin A.E., 2000). Patient in the acute phase of cerebral ischaemic stroke (CIS) are found to have decreased levels of NO2 (a stable metabolite of NO), which indicates the participation of endothelium-dependent mechanisms in the pathogenesis of CIS. Impairment of the vasomotor function of the endothelium is enhanced as the clinical symptoms deteriorate in patients with CIS (Malakhov V.A., Zavgorodnyaya A.N., 2007).

One of the main reasons for decreased EDVD in patients with coronary heart disease (CHD) is hypercholesterolemia, since the latter accelerates apoptosis in endotheliocytes and decreases endothelial synthesis of NO (Movchan E.A., 2008).

NO controls various pulmonary functions, such as the activity of macrophages, bronchoconstriction and dilatation of pulmonary arteries. Patients with pulmonary hypertension (PH) are found to have reduced pulmonary NO levels. One of the causes of this condition is impaired metabolism of L-arginine. Thus, patients with arterial PH are found to have association of decreased L-arginine levels with elevated arginase activity. Also, impaired pulmonary metabolism of ADMA may initiate, stimulate or maintain chronic pulmonary disease, including arterial PH. Elevated ADMA levels are found in patients with idiopathic arterial PH, chronic thromboembolic PH, as well as arterial PH, associated with sickle cell anaemia or systemic sclerosis (Maarsingh H. et al., 2008; Zakrzewicz D., Eickelberg O., 2009).

Due to the huge pool of endothelial cells in the glomerular capillaries, endothelial function substantially determines the regulation of vascular tone in the kidneys. The role of endothelium in the regulation of vascular tone and renal haemodynamic is mediated by the interaction of the potent vasoactive factors it produces. The redistribution of the balance of vasoactive factors in favour of vasoconstrictors not only initiates the development of nephrosclerosis, decreased glomerular filtration rates and renal perfusion, but also precipitates the onset of AH (Movchan E.A., 2008).

NO is of special significance in clinical pathophysiology of the kidneys. There is evidence supporting the continuous synthesis of NO in endothelial and smooth muscle cells of renal vessels, as well as epithelial and mesangial cells of the tubules; owing to that NO plays an important role

in regulation of renal perfusion, the excretory function of the kidneys and the tubulo-glomerular balance. These effects are partially implemented by interaction of NO with the renin-angiotensin system and other bioregulators of renal function. Decreased production and function of NO, in part, in the vascular endothelium, is closely related with the pathogenesis of reduction of renal tissue due to kidney damage. There are various mechanisms behind this deficiency, including reduction of NO synthesis due to decreased concentration or activity of renal cortical nNOS, as well as reduction in active dimers of eNOS due to degradation of tetrahydrobiopterin, a cofactor of eNOS; increase in circulating ADMA (plasma ADMA levels correlate with the severity of chronic kidney disease); limited availability of substrate (L-arginine) due to the decrease of its renal synthesis or impaired transport into the cell; impaired renal tubular regeneration of arginine; utilization of arginine by arginase; inactivation of NO by reactive oxygen species (ROS). Furthermore, accumulation of the end products of glycosylation in progressing renal disease impedes the access of NO to its targets (Markov Kh.M., 2000; Baylis C., 2008; Ohkita M. et al., 2009).

Physiological vascular adaptation to pregnancy (increase of circulating blood volume, cardiac output and a reduction in vascular resistance) is accompanied by an increase in endogenous NO production and increased susceptibility of smooth muscle cells of the vessels to NO. Experimental studies have demonstrated the role of increased oxidative stress and reduced bioavailability of such vasodilators as NO in the pathogenesis of cardiovascular dysfunction during pregnancy; in vitro preeclampsia studies have demonstrated impaired EDVD of isolated umbilical arteries. Preeclampsia is also accompanied by increased haemoglobin levels; the latter viewed as an acceptor of NO (Buhimschi I.A. et al., 1998; Gilbert J.S. et al., 2008).

Current evidence concerning the efficacy of arginine as a nitric oxide donator

Increased production and release of NO, mediated by L-arginine, may promote antioxidation and facilitate improved endothelial function in patients with hypercholesterolemia. In a double-blind, placebo-controlled study in 43 patients aged 57±10 years with hypercholesterolemia and impaired flow-mediated dilation (FMD), A.J. Maxwell et al. (2000) found positive changes of EDVD with oral L-arginine at 6-21 g/day. The vasodilating function of the endothelium improved from 6,5±3 to 10±5%. In a study by H. Kawano et al. (2002) 17 males with hypercholesterolemia (mean age - 41,7 years) were found to have increased flow-mediated dilation (from 3,92±0,58 to 7,27±0,53%; $p<0,01$) in 1 h post-infusion (30g of L-arginine infused over 1 h), as well as decreased markers of lipid peroxidation (thiobarbituric acid reactive substances, TBARS) from 5,45±0,43 to 4,83±0,35 nmol/mL; $p<0,01$). In a randomized, placebo-controlled crossover study in 16 middle-aged patients with hypercholesterolemia, S.G. West et al. (2005) have demonstrated that oral L-arginine at 12 g/day administered for 3 weeks contributed to reduction of diastolic BP (DBP) by 1,9 mm Hg, reduction of plasma homocysteine by 2 μmol/L and increased period of tension of the cardiac ventricles by 3,4 msec. Using a combination of 1,5 g of L-arginine with simvastatin at the dose of 20 mg/day in a randomized, double-blind study enrolling 33 patients with hypercholesterolemia produced a significant decrease in triglycerides compared to the patients receiving only simvastatin (by 140,5±149,2 and by 56,1±85 mg/dL respectively; $p=0,048$) (F. Schulze et al., 2009).

The oxidized cholesterol of low-density lipoproteins (LDL) increases the expression of arginase and reduces the level of eNOS in endothelial cells, leading to decreased production of NO. A randomized, crossover study by W.H. Yin et al. (2005) has demonstrated improved endothelial function and reduced LDL oxidation in 31 patients with stable angina in oral administration of L-arginine at 10 g/day for 4 weeks. T. Lauer et al. (2008) have demonstrated increased minimal diameter of the vascular lumen in a stenotic segment from 0,98±0,06 to 1,14±0,07mm ($p<0,05$) without the influence on other segments in patients with CHD when administering L-arginine at 150 μmol/min. The blood flow in the post-stenotic segment has increased by 24±3%. In a randomized crossover study enrolling 42 patients with stable effort angina of functional class (FC)

I-II, A.V. Sozykin et al. (2000) have found substantial improvements of endothelial function (from 5,0±2,9 to 7,8±4,1%) and exercise tolerance and decreased platelet aggregation (in 17 patients of 20) in the group receiving L-arginine 15 g/day for 10 days. A. Palloshi et al. (2004), after assessment of 13 patients with microvascular angina, receiving 2 g of L-arginine 3 times a day for 4 weeks, have noted improvement in the FC of angina, improved BP (SBP) at rest, improved quality of life, increased concentrations of L-arginine and cGMP and the L-arginine/ADMA ratio.

A. Jabłecka et al. (2004), after assessment of 32 patients with atherosclerotic lesions of peripheral arteries Stage II and III after Fontaine, have found a substantial elevation of NO levels and improvement of total antioxidant status (TAS) due to administration of L-arginine at the dose of 2 or 4 g t.i.d. for 28 days. In a randomised study by R.K. Oka et al. (2005), enrolling 80 patients with peripheral artery lesions and intermittent claudication, receiving L-arginine at the daily doses of 3,6 or 9 g/day in 3 divided doses for 12 weeks, a trend towards increased walking speed was found. A more pronounced increase in walking distance was found in the group receiving L-arginine at the dose of 3 g/day. The drug was well tolerated; no serious adverse events were documented.

Aging and various risk factors of cardiovascular disease are also associated with oxidative stress and endothelial dysfunction. M.P. Schlaich et al. (2007), having assessed 23 young males (mean age 30±5 years) with high risk of cardiovascular disease (impaired lipid metabolism and increased BP), have estimated increased renal plasma flow (by 123±64,4 mL/min compared to 75,6±60,2 mL/min in the control group) after infusion of L-arginine 100 mg/kg. Elderly subjects with CVD have diminished flow-mediated dilation of brachial artery and decreased bioavailability of NO. In a prospective, double-blind, randomized, crossover study enrolling 12 healthy volunteers aged 73,8 ± 2,7 years S.M. Bode-Böger et al. (2003) have demonstrated that oral L-arginine, administered for 14 days at the dose of 8 g b.i.d. Significantly increases flow-mediated dilation of the artery (by 5,7±1,2%) and normalises the L-arginine/ADMA ratio ($p<0,05$).

Smoking decreases NO content due to increased oxidative stress, also increasing monocyte adhesion susceptibility of LDL to oxidation. In a randomized, placebo-controlled, double-blind, crossover study enrolling 12 healthy smokers G. Siasos et al. (2009) have found the use of 7g of L-arginine t.i.d. to prevent smoking-induced an increase in pulse wave velocity between brachium and the right ankle, as well as an increase in augmentation index; the treatment was also found to decrease the serum levels of sICAM-1 (the soluble form of intercellular adhesion molecule-1).

The domestic experience of using L-arginine is equally interesting: V.A. Slobodsky from the National Science Centre 'Institute of Cardiology named after Academician ND Strazhesko' of the AMS of Ukraine (2009) evaluated the effects of oral solution of L-arginine aspartate, Tivortin aspartate (by Yuria-Pharm) in 38 out-patients with CHD and stable effort angina of II-III FC. The drug was used concomitantly to conventional treatment at 15 mL (1,71 g) 2 times a day for 2 months. The results of the study have shown improved endothelial function, exercise tolerance and quality of life in the patients. Administration of the drug has significantly improved EDVD (from 3,35±0,48 to 6,24±0,41; $p<0,01$); time to ECG signs of ischemia and/or pain in graduated exercise testing has increased (from 7,18±0,64 to 9,62±0,61 minutes; $p<0,05$); also, there was a 34% improvement of overall performance ($p<0,05$). Nitro-glycerine requirement have decreased from 3,61±0,5 to 1,1±0,24 tablets per day ($p<0,01$).

The influence of oral L-arginine 15 g/day on renal haemodynamic during a 5-day period was evaluated in a randomized, double-blind, crossover study enrolling 17 patients aged 56 ± 12 years with chronic congestive heart failure (CHF) II-III FC according to NYHA (New York Heart Association) G. Watanabe et al. (2000). The authors have found an increase in daily excretion of cGMP (from 0,8±0,5 to 1,4±1,1 μmol/day; $p<0,01$) and daily creatinine clearance (from 125±42 to 150±43 mL/min; $p<0,05$), as well as decreased plasma endothelin levels (from 3,1±0,8 to 2,5±0,6 pg/mL; $p<0,05$). Besides, a relative increase in urinary sodium excretion and glomerular

filtration rate was noted in response to the load by NaCl solution compared to the group of placebo (47±12% vs. 34±9% and 44±31% vs. 22±29%, respectively; p<0,05).

In a study by E.A. Bocchi et al. (2000) enrolling 7 patients (age 39 ± 8 years) with severe congestive heart failure intravenous administration of L-arginine (at the mean dose of 30,4 ± 1,9 g) led to a reduction in heart rate (from 88±15 to 80±16 bpm; p<0,005), mean systemic BP (from 84±17 to 70±18 mm Hg; p<0,007) and systemic vascular resistance (from 24±8 to 15±6 Wood units; p<0,003); an increase in cardiac output (from 3,4±0,7 to 4,1±0,8 L/min; p<0,009) and systolic blood volume (from 40±9 to 54±14 mL; p<0,008). B. Bednarz et al. (2004) reported increased exercise tolerance (99±103 compared to 70±99 in the group receiving placebo) in the patients (21 subjects) with CHF II-III FC according to NYHA after oral intake of L-arginine 9g/day for 7 days.

In a prospective, randomized, double-blind trial enrolling 35 patients with AH, J.P. Lekakis et al. (2002) found an improvement of flow-mediated EDVD in administration of 6 g of L-arginine. Treatment with L-arginine has substantially improved flow-mediated dilation of brachial artery (1,7±3,4 vs. 5,9±5,4%; p=0,008).

The bioavailability of NO is reduced in myocardial infarction. B. In a multicentre, randomized, double-blind, placebo-controlled study enrolling 792 patients (mean age 64 years; 551 male subjects), who initiated oral L-arginine at 3g t.i.d for 30 days 24h post ST-elevation MI, Bednarz et al. (2005) have found a positive trend concerning newly occurred clinically significant events (in 24% patients vs. 27% patients in the placebo group). The therapy with L-arginine was well tolerated.

Patients with acute coronary syndrome are found to have marked activation of peripheral T-lymphocytes, increases acute phase proteins and increased oxidative stress. J. George et al. (2004), after examining patients with unstable angina undergoing percutaneous coronary procedure (PCP) with stenting, have found reduced systemic growth of activation of peripheral T lymphocytes and markers of oxidative stress, caused by damage of the vascular wall in course of PCP in 1 months of therapy by L-arginine at the dose of 6g/day, initiated immediately after stent placement. P. In a randomized, double-blind study enrolling 64 patients with CVD without Type 2 DM who underwent coronary artery bypass grafting (CABG), Lucotti et al. (2009) have found decreased ADMA levels (p<0,01) and decreased indices of ED along with increased cGMP levels (p<0,01) and L-arginine/ADMA ratio (p<0,0001) in oral intake of L-arginine at the dose of 6,4 g/day for 6 months. Also, increases in insulin sensitivity index (p<0,05) and adiponectin levels (p<0,01) were documented, as well as reduced levels of IL-6 and MCP-1.

Both ED and decreased bioavailability of NO are regarded as possible reasons for the failure of therapeutic angiogenesis and cell therapy. Post-CABG patients with CHD with simultaneous involvement of 3 vessels and severe diffuse damage to the left anterior descending artery M. Ruel et al. (2008) found improved perfusion and anterior myocardial contractility along with a trend towards less perfusion defects after the course of 10 injections of vascular endothelial growth factor in combination with oral L-arginine at 6g/day for 3 months.

The effect of L-arginine on the response of cerebral vessels to CO2 has been investigated by C. Zimmermann and R.L. Haberl (2003), who have found a substantial increase of vasomotor response (from 42±8 to 52±14%; p=0,005) after the infusion 30g of L-arginine in 22 patients at risk for CVD and compromised vasomotor responses (<50%) in the absence of extra -and intracranial stenoses. In a 2004 study C. Zimmermann et al. have found average flow velocity to increase by 28±10% compared to 22±10% in the control group after the infusion of 30g of L-arginine in 55 patients (mean age – 63 ± 8,5 years) at risk for CVD. Notably, patients with a history of stroke or TIA were found to have a stronger response to L-arginine compared to patients without prior cerebrovascular events. M. Okamoto et al. (2001), having assessed 20 elderly patients (mean

age –70,2 ± 2,8 years), have found mean BP to decrease and cerebral blood flow to increase after intravenous infusion of 500 mg/kg of L-arginine monohydrochloride for 30 min.

Recently there were several studies of L-arginine efficacy in hereditary syndromes, associated with stroke. Y. Toribe et al. (2007) in intravenous administration of L-arginine (0,5g/kg body weight) in 5 hours after the onset of status epilepticus in a patient with MELAS syndrome (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and cerebral ischaemic episodes — mitochondrial myopathy, encephalopathy, lactic acidosis, cerebral ischemic episodes) have found pathological encephalographic findings to subside and the duration of status epilepticus to shorten. Also, there was a rapid clinical recovery with shorter hospital stay. F. Moutaouakil et al. (2009) have reported complete and rapid disappearance of cerebral ischemic episodes in a 12-year old child with MELAS syndrome after oral use of L-arginine at the dose of 0,4 mg/kg of body weight per day.

N. Nagaya et al. (2001) have found a positive influence of L-arginine on haemodynamic and exercise tolerance in patients with precapillary pulmonary hypertension, receiving oral L-arginine at 0,5g/10 kg of body weight 3 times a day in a randomized, double-blind, placebo-controlled study (19 subjects). A substantial elevation of plasma L-citrulline levels was found, which was indicative of increased production of NO, a 9% decrease of mean pulmonary arterial pressure (from 53±4 to 48±4 mm Hg; $p<0,05$) and a 16% decrease of pulmonary vascular resistance (from 14,8±1,5 to 12,4±1,4 Wood units; $p<0,05$), as well as a moderate decrease in systemic BP (from 92±4 to 87±3 mm Hg; $p<0,05$). Using L-arginine for 1 week has led to an insignificant increase in maximal oxygen consumption (from 831±88 to 896±92 mL/min; $p<0,05$) and significant decrease of the slope of the curve of the relationship of minute ventilation on carbon dioxide production (VE/VCO2 slope) (from 43±4 to 37±3; $p<0,05$).

The efficacy of using L-arginine in complicated course of pregnancy was found in several studies.

F. Facchinetti et al. (2007), on assessment of 28 patients with preeclampsia and 46 patients with gestational hypertension, randomised into the groups of placebo or intravenous L-arginine at 20 g/day for 5 days with subsequent oral L-arginine at 4 g/day for 2 weeks, have noted a substantial decrease of SBP and DBP in 6 days after treatment in the group receiving L-arginine. Also, there was a trend towards prolonged pregnancy. In a prospective, randomized, placebo-controlled study enrolling 61 pregnant women with preeclampsia, receiving a standardized diet with reduced nitrogen content and L-arginine 3 g/day for 3 weeks complimentary to standard therapy, K. Rytlewski et al. (2005) have found a a significant reduction in SBP levels (up to 134,2±2,9 vs. 143,1 ±2,8 mm Hg at baseline; $p<0,01$), DBP (up to 81,6±1,7 vs. 86,5±0,9 mm Hg at baseline ; $p<0,01$), mean BP (up to to 101,8±1,5 vs. 108,0±1,2 mm Hg at baseline; $p<0,01$) on the background of increasing daily excretion of NO metabolites (NO2- and NO3-) and plasma L-citrulline levels. I. Neri et al. (2006) have noted a decrease in SBP and DBP after intravenous administration of 20g of L-arginine in 62 pregnant women with gestational hypertension (age – 16-45 years old) at the terms of 24-36 weeks (32,2% were receiving antihypertensive treatment before the study). L-arginine was well tolerated.

L-arginine promotes the intrauterine growth of the foetus by increasing NO production and improving circulation of blood in the umbilical artery. In a randomized, placebo-controlled, double-blind clinical trial enrolling 83 pregnant women with preeclampsia K. Rytlewski et al. (2006) have found a significant decrease of the pulsatility index of the umbilical artery in the patients, receiving L-arginine 3 g/day complimentary to standard therapy, starting from the third week of therapy. Therapy by L-arginine contributed to a substantial increase in the pulsatility index of the middle cerebral artery and cerebro-placental ratio. The duration of pregnancy and the Apgar score of the neonates was also higher in the treatment group. N. Zhang et al. (2007), having

performed assessments of 25 pregnant women with gestational hypertension and intrauterine foetal growth retardation (IFGR), who received L-arginine complimentary to standard therapy, found a notable decrease of the systolic/diastolic ratio, pulse index and resistance index. The levels of NO in both maternal and foetal blood were significantly higher than in the group receiving standard therapy only. Body weight of neonates born to mothers receiving L-arginine was at the level of the control group (2,9±0,3 vs. 3±0,3 kg; p=0,18) and was substantially higher than in the group receiving standard therapy (2,7±0,3 kg; p=0,006). These data complement the results of a study by P. Sieroszewski et al. (2004), in which 78 pregnant women with established IFGR received oral L-arginine at 3 g/day for 20 days: in the group receiving L-arginine, there was a higher body weight at birth (mean body weight - 2823g vs. 2495g in the group not using L-arginine; p=0,027); the portion of the neonates with intrauterine growth retardation was lower (29% vs. 73% in the group not using L-arginine). X.M. Xiao and L.P. Li (2005), having performed assessments of 30 pregnant women with asymmetric form of IFGR, have found that using L-arginine complimentary to standard therapy caused a significant increase of NO2- and NO3- levels in maternal serum (p<0,01), as well as body weight of the neonate (p<0,05) compared to the group of patients receiving standard therapy only.

Thus, the results of numerous recent studies, which we tried to summarise in this paper, indicate the possibility of an effective and safe clinical use of L-arginine as an active donator of NO in order to treat various disease.

References

Original sources	English translation (where applicable)
Белоусов Ю.Б., Намсараев Ж.Н. (2004) Эндотелиальная дисфункция как причина атеросклеротического поражения артерий при артериальной гипертензии: методы коррекции. Фарматека, 6(84): 62-72.	Belousov Yu.B., Namsaraev Zh.N. (2004) Endothelial dysfunction as a cause of atherosclerotic arterial lesions in hypertension: the methods of correction. Pharmauteca, 6(84): p. 62-72.
Визир В.А., Березин А.Е. (2000) Роль эндотелиальной дисфункции в формировании и прогрессировании артериальной гипертензии. Прогностическое значение и перспективы лечения. Укр. мед. часопис, 4(18): 23-33 (http://www.umj.com.ua/ rus/archive/18/1056.html; http://www.umj.com.ua/archive/18/pdf/1056_rus.pdf).	Vizir B.A., Berezin A.E. (2000) The role of endothelial dysfunction in the emergence and progression of hypertension. Prognostic value and treatment perspectives. Ukr. Med. J., 4(18): p.23-33 (http://www.umj.com.ua/ rus/archive/18/1056.html; http://www.umj.com.ua/archive/18/pdf/1056_rus.pdf).
Головченко Ю.И., Трещинская М.А. (2008) Обзор современных представлений об эндотелиальной дисфункции. Consilium medicum Ukraina, 11: 38-40.	Golovchenko Yu.I., Treshinskaya M.A. (2008) Review of modern concepts of endothelial dysfunction. Consilium medicum Ukraina, 11: p.38-40.
Гуревич М.А., Стуров Н.В. (2006) Дефицит nitric oxide и поддержание сосудистого гомеостаза: роль мононитратов и проблемы цитопротекции. Трудный пациент, 3: 23-29.	Gurevich M.A., Sturov N.V. (2006) Nitric oxide deficiency and maintenance of vascular homeostasis: the role of mononitrates and problems of cytoprotection. Challenging Patient J. (Trudnyi Patsient), 3: p.23-29.
Ельский В.Н., Ватутин Н.Т., Калинкина Н.В., Салахова А.М. (2008) Роль дисфункции эндотелия в генезе сердечно-сосудистых заболеваний. Журн. АМН України, 14(1): 51-62.	Elskyi V.N., Vatutin N.T., Kalinkina N.V., Салахова A.M. (2008) The role of endothelial dysfunction in the genesis of cardiovascular disease. The Journal of The Academy of Sciences of Ukraine, 14(1): p.51-62.
Малахов В.А., Завгородняя А.Н. (2007) Система nitric oxide при церебральном ишемическом инсульте: некоторые патогенетические аспекты. Укр. мед. часопис, 2(58): 97-100 (http:// www.umj.com.ua/archive/58/149.html; http://www.umj.com.ua/archive/58/pdf/149_rus.pdf).	Malakhov V.A., Zavgorodnyaya A.N. (2007) the system of nitric oxide in cerebral ischemic stroke: certain pathogenetic aspects. Ukr. Med. J., 2(58): 97-100 (http:// www.umj.com.ua/archive/58/149.html; http://www.umj.com.ua/archive/58/pdf/149_rus.pdf).
Марков Х.М. (2000) Роль nitric oxide в па-тогенезе болезней детского возраста. Рос. вестн. перинатол. и педиатр., 4: 43-47.	Markov Kh.M. (2000) The role of nitric oxide in the pathogenesis of paediatric disease. Russian Bulletin of Perinatology and Paediatrics, 4: p.43-47.
Мовчан Е.А. (2008) Дисфункция эндотелия и тромбоцитов при хронической болезни почек: новый взгляд на старую проблему нарушений в системе гемостаза у больных гломерулонефритом. Бюллетень сибирской медицины, Приложение 2: 88-96.	Movchan E.A. (2008) The dysfunction of the endothelium and platelets in chronic renal disease: a new understanding of an old problem of impaired haemostasis in patients with glomerulonephritis. The Bulletin of Siberian Medicine, Appendix 2: p.88-96.
Слободський В.А. (2009) Досвід застосування препарату Тівортін® аспартат при лікуванні пацієнтів зі стабільною стенокардією напруження. Укр. мед.	Slobodskyi V.A. (2009) The experience of using the product Tivortin® aspartate in treatment of patients

часопис, 5(73): 40-43 (http://www.umj. com.ua/archive/73/1511.html; http://www.umj.com.ua/archive/73/pdf/1511_ukr.pdf).	with stable effort angina. Ukr. Med. J., 5(73): p.40-43 (http://www.umj. com.ua/archive/73/1511.html; http://www.umj.com.ua/archive/73/pdf/1511_ukr.pdf).
Созыкин А.В., Ноева Е.А., Балахонова Т.В. и др. (2000) Влияние L-arginine на агрегацию тромбоцитов, функцию эндотелия и толерантность к физической нагрузке у пациентов со стабильной стенокардией напряжения. Тер. архив, 72(8): 24-27.	Sozykin A.V., Noeva E.A., Balakhonova T.V. et al. (2000) The influence of L-arginine on platelet aggregation, endothelial function and exercise tolerance in patients with stable effort angina. The Therapeutic Archive, 72(8): p.24-27.
Степанов Ю.М., Кононов И.Н., Журбина А.И., Филиппова А.Ю. (2004) Аргинин в медицинской практике. Журн. АМН України, 10(1): 340-352.	Stepanov Yu.M., Kononov I.N., Zhurbina A.I., Filippova A.Yu. (2004) Arginine in medical practice. The Journal of The Academy of Sciences of Ukraine, 10(1): 340-352.
Baylis C. (2008) Nitric oxide deficiency in chronic kidney disease. Am. J. Physiol. Renal Physiol., 294: 1-9.	N/A
Bednarz B., Jaxa-Chamiec T., Gebalska J. et al. (2004) L-arginine supplementation prolongs exercise capacity in congestive heart failure. Kardiol. Pol., 60(4): 348-353.	N/A
Bednarz B., Jaxa-Chamiec T., Maciejewski P. et al. (2005) Efficacy and safety of oral L-arginine in acute myocardial infarction. Results of the multicenter, randomized, double-blind, placebo-controlled ARAMI pilot trial. Kardiol. Pol., 62(5): 421-427.	N/A
Bocchi E.A., Vilella de Moraes A.V., Esteves-Filho A. et al. (2000) L-arginine reduces heart rate and improves hemodynamics in severe congestive heart failure. Clin. Cardiol., 23(3): 205-210.	N/A
Bode-Böger S.M., Muke J., Surdacki A. et al. (2003) Oral L-arginine improves endothelial function in healthy individuals older than 70 years. Vasc. Med., 8(2): 77-81.	N/A
Böger R.H. (2007) The pharmacodynamics of L-arginine. J. Nutr., 137: 1650S-1655S.	N/A
Bryan N.S., Bian K., Murad F. (2009) Discovery of the nitric oxide signaling pathway and targets for drug development. Frontiers in Bioscience, 14: 1-18.	N/A
Buhimschi I.A., Saade G.R., Chwalisz K., Garfield R.E. (1998) The nitric oxide pathway in pre-eclampsia: pathophysiological implications. Human Reproduction Update, 4(1): 25-42.	N/A
Chatterjee A., Catravas J.D. (2008) Endothelial nitric oxide (NO) and its pathophysiologic regulation. Vascul. Pharmacol., 49(4-6): 134-140.	N/A
Facchinetti F., Saade G.R., Neri I. et al. (2007)L-arginine supplementation in patients with gestational hypertension: a pilot study. Hypertens Pregnancy, 26(1): 121-130.	N/A
George J., Shmuel S.B., Roth A. et al. (2004) L-arginine attenuates lymphocyte activation and anti-oxidized LDL antibody levels in patients undergoing angioplasty. Atherosclerosis, 174(2): 323-327.	N/A
Gilbert J.S., Nijland M.J., Knoblich P. (2008) Placental ischemia and cardiovascular dysfunction in preeclampsia and beyond: making the connections. Expert Rev. Cardiovasc. Ther., 6(10): 1367-1377.	N/A
Gkaliagkousi E., Ritter J., Ferro A. (2007) Platelet-derived nitric oxide signaling and regulation. Circ. Res., 101(7): 654-662.	N/A
Gornik H.L., Creager M.A. (2004) Arginine and endothelial and vascular health. J. Nutr., 134: 2880S- 2887S.	N/A
Jablecka A., Checiński P., Krauss H. et al. (2004) The influence of two different doses of L-arginine oral supplementation on nitric oxide (NO) concentration and total antioxidant status (TAS) in atherosclerotic patients. Med. Sci. Monit., 10(1): CR29-32.	N/A
Kawano H., Motoyama T., Hirai N. et al. (2002) Endothelial dysfunction in hypercholesterolemia is improved by L-arginine administration: possible role of oxidative stress. Atherosclerosis, 161(2): 375-380.	N/A
Lauer T., Kleinbongard P., Rath J. et al. (2008) L-arginine preferentially dilates stenotic segments of coronary arteries thereby increasing coronary flow. J. Intern. Med., 264(3): 237-244.	N/A
Lekakis J.P., Papathanassiou S., Papaioannou T.G. et al. (2002) Oral L-arginine improves endothelial dysfunction in patients with essential hypertension. Int. J. Cardiol., 86(2-3): 317-323.	N/A

Lubos E., Handy D.E., Loscalzo J. (2009) Role of oxidative stress and nitric oxide in atherothrombosis. Front. Biosci., 13: 5323-5344. N/A	N/A
Lucotti P., Monti L., Setola E. et al. (2009) Oral L-arginine supplementation improves endothelial function and ameliorates insulin sensitivity and inflammation in cardiopathic nondiabetic patients after an aortocoronary bypass. Metabolism, 58(9): 1270-1276.	N/A
Maarsingh H., Pera T., Meurs H. (2008) Arginase and pulmonary diseases. Naunyn-Schmiedberg's Arch. Pharmacol., 378: 171-184.	N/A
Maxwell A.J., Anderson B., Zapien M.P., Cooke J.P. (2000) Endothelial dysfunction in hyper-cholesterolemia is reversed by a nutritional product designed to enhance nitric oxide activity. Cardiovasc. Drugs Ther., 14(3): 309-316.	N/A
Moutaouakil F., El Otmani H., Fadel H. et al. (2009) L-arginine efficiency in MELAS syndrome. A case report. Rev. Neurol. (Paris), 165(5): 482-485.	N/A
Nagaya N., Uematsu M., Oya H. et al. (2001) Short-term oral administration of L-arginine improves haemodynamic and exercise capacity in patients with precapillary pulmonary hypertension. Am. J. Respir. Crit. Care Med., 163(4): 887-891.	N/A
Neri I., Jasonni V.M., Gori G.F. et al. (2006) Effect of L-arginine on blood pressure in pregnancy- induced hypertension: a randomized placebo-controlled trial. J. Matern. Fetal Neonatal. Med., 19(5): 277-281.	N/A
Ohkita M., Takaoka M., Matsumura Y. (2009) Drug discovery for overcoming chronic kidney disease (CKD): the endothelin ETB receptor / nitric oxide system functions as a protective factor in CKD. J. Pharmacol. Sci., 109: 7-13.	N/A
Oka R.K., Szuba A., Giacomini J.C., Cooke J.P. (2005) A pilot study of L-arginine supplementation on functional capacity in peripheral arterial disease. Vasc. Med., 10(4): 265-274.	N/A
Okamoto M., Etani H., Yagita Y. et al. (2001) Diminished reserve for cerebral vasomotor response to L-arginine in the elderly: evaluation by transcranial Doppler sonography. Gerontology, 47(3):131-135.	N/A
Palloshi A., Fragasso G., Piatti P. et al. (2004) Effect of oral L-arginine on blood pressure and symptoms and endothelial function in patients with systemic hypertension, positive exercise tests, and normal coronary arteries. Am. J. Cardiol., 93(7): 933-935.	N/A
Paszkowiak J.J., Dardik A. (2003) Arterial wall shear stress: observations from the bench to the bedside. Vascular and Endovascular Surgery, 37(1): 47-57.	N/A
Ruel M., Beanlands R.S., Lortie M. et al. (2008) Concomitant treatment with oral L-arginine improves the efficacy of surgical angiogenesis in patients with severe diffuse coronary artery disease: the Endothelial Modulation in Angiogenic Therapy randomized controlled trial. J. Thorac. Cardiovasc. Surg., 135(4): 762-770.	N/A
Rytlewski K., Olszanecki R., Korbut R., Zdebski Z. (2005) Effects of prolonged oral supple-mentation with l-arginine on blood pressure and nitric oxide synthesis in preeclampsia. Eur. J. Clin. Invest., 35(1): 32-37.	N/A
Rytlewski K., Olszanecki R., Lauterbach R. et al. (2006) Effects of oral L-arginine on the foetal condition and neonatal outcome in preeclampsia: a preliminary report. Basic Clin. Pharmacol. Toxicol., 99(2): 146-152.	N/A
Schlaich M.P., Oehmer S., Schneider M.P. et al. (2007) Effects of nitric oxide synthase inhibition and L-arginine on renal haemodynamics in young patients at high cardiovascular risk. Atherosclerosis, 192(1): 155-160.	N/A
Schulze F., Glos S., Petruschka D. et al. (2009) L-Arginine enhances the triglyceride-lowering effect of simvastatin in patients with elevated plasma triglycerides. Nutr. Res., 29(5): 291-297.	N/A
Siasos G., Tousoulis D., Vlachopoulos C. et al. (2009) The impact of oral L-arginine supplementation on acute smoking-induced endothelial injury and arterial performance. Am. J. Hypertens., 22(6): 586-592.	N/A
Sieroszewski P., Suzin J., Karowicz-Bilińska A. (2004) Ultrasound evaluation of intrauterine growth restriction therapy by a nitric oxide donor (L-arginine). J. Matern. Fetal Neonatal Med., 15(6): 363-366.	N/A
Toribe Y., Tominaga K., Ogawa K., Suzuki Y. (2007) Usefulness of L-arginine infusion for status epilepticus in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes. No To Hattatsu., 39(1): 38-43.	N/A
Visek W.J. (1986) Arginine needs, physiological state and usual diets. A re-evaluation. J. Nutr., 116: 36-46.	N/A
Watanabe G., Tomiyama H., Doba N. (2000) Effects of oral administration of L-arginine on renal function in patients with heart failure. J. Hypertens., 18(2): 229-234.	N/A

West S.G., Likos-Krick A., Brown P., Mariotti F. (2005) Oral L-arginine improves hemodynamic responses to stress and reduces plasma homocysteine in hypercholesterolemic men. J. Nutr., 135(2): 212-217.	N/A
Wu G., Morris S.M. Jr. (1998) Arginine metabolism: nitric oxide and beyond. Biochem. J., 336: 1-17.	N/A
Xiao X.M., Li L.P. (2005) L-Arginine treatment for asymmetric fetal growth restriction. Int. J. Gynaecol. Obstet., 88(1): 15-18.	N/A
Yi J., Horky L.L., Friedlich A.L. et al. (2009) L-Arginine and Alzheimer's disease. Int. J. Clin. Exp. Pathol., 3: 211-238.	N/A
Yin W.H., Chen J.W., Tsai C. et al. (2005) L-arginine improves endothelial function and reduces LDL oxidation in patients with stable coronary artery disease. Clin. Nutr., 24(6): 988-997.	N/A
Zakrzewicz D., Eickelberg O. (2009) From arginine methylation to ADMA: A novel mechanism with therapeutic potential in chronic lung diseases. BMC Pulmonary Medicine, 9: 5.	N/A
Zhang N., Xiong A.H., Xiao X., Li L.P. (2007) Effect and mechanism of L-arginine therapy for fetal growth retardation due to pregnancy-induced hypertension. Nan. Fang Yi Ke Da Xue Xue Bao, 27(2): 198-200	N/A
Zimmermann C., Haberl R.L. (2003) L-arginine improves diminished cerebral CO_2 reactivity in patients. Stroke, 34(3): 643-647.	N/A
Zimmermann C., Wimmer M., Haberl R.L. (2004) L-arginine-mediated vasoreactivity in patients with a risk of stroke. Cerebrovasc. Dis., 17(2-3): 128-133.	N/A