The Effects of a Sustained-Release L-Arginine Formulation on Blood Pressure and Vascular Compliance in 29 Healthy Individuals

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Abstract

Vascular endothelial function is crucial to cardiovascular function and thus to blood perfusion to the heart and throughout the body. A number of substances are produced and secreted by vascular endothelial cells, the most important of which is nitric oxide, a potent regulator of vascular function. Nitric oxide diffuses from endothelial cells into underlying smooth muscle, causing relaxation, which results in vasodilation. When this process is inhibited or inadequate the arteries cannot dilate as necessary, resulting in hypertonicity and reduced blood flow. Such endothelial dysfunction also causes increased platelet and monocyte adhesiveness and smooth muscle proliferation, processes thought to be at the genesis of atherosclerotic plaque formation. Since L-arginine is the body's only substrate for nitric oxide synthesis, adequate L-arginine must be present for proper nitric oxide production.

In this open label trial, a group of 29 asymptomatic individuals were given L-arginine (1,050 mg, as Perfusia-SR®, a sustained-release preparation) twice daily (total 2.1 g daily) for one week. Systolic blood pressure was reduced in 62 percent of participants compared to baseline, with a non-significant mean decrease in all patients of 4 mmHg. Diastolic blood pressure was reduced in 69 percent of participants, with a mean reduction of 3.7 mmHg (p=0.005). In the 10 individuals who were borderline or hypertensive (systolic >130 or diastolic >85), there was a mean systolic reduction of 11 mmHg (p=0.05), while normotensives (n=19) had a mean systolic decrease of only 0.22 mmHg. Diastolic blood pressure was decreased a non-significant 4.9 mmHg in borderline or hypertensives and 4.5 mmHg in normotensives (p=0.026).

Vascular elasticity relates to endothelial function, and can be measured non-invasively. At baseline and follow-up, vascular compliance was assessed via digital pulse wave analysis (DPA; Meridian Medical). After one week, pulse wave analysis showed a significant increase in large artery compliance (mean 23% improvement; p=0.02) and a non-significant increase in small artery compliance (mean 23% improvement; p=0.15).

This study demonstrates blood pressure reductions, especially in patients with borderline or frank hypertension, as well as improved vascular compliance – an indicator of improved endothelial function and perfusion – after a one-week trial of sustained-release L-arginine. Poor endothelial function due to inadequate endothelial nitric oxide production is present in hypertension, as well as in numerous other aspects of cardiovascular disease, including angina, erectile dysfunction, cerebrovascular disease, and peripheral vascular disease. This is the first study showing a moderate dose of sustained-release L-arginine can improve endothelial function and blood pressure. ***(Altern Med Rev* 2006;11(1):23-29)**

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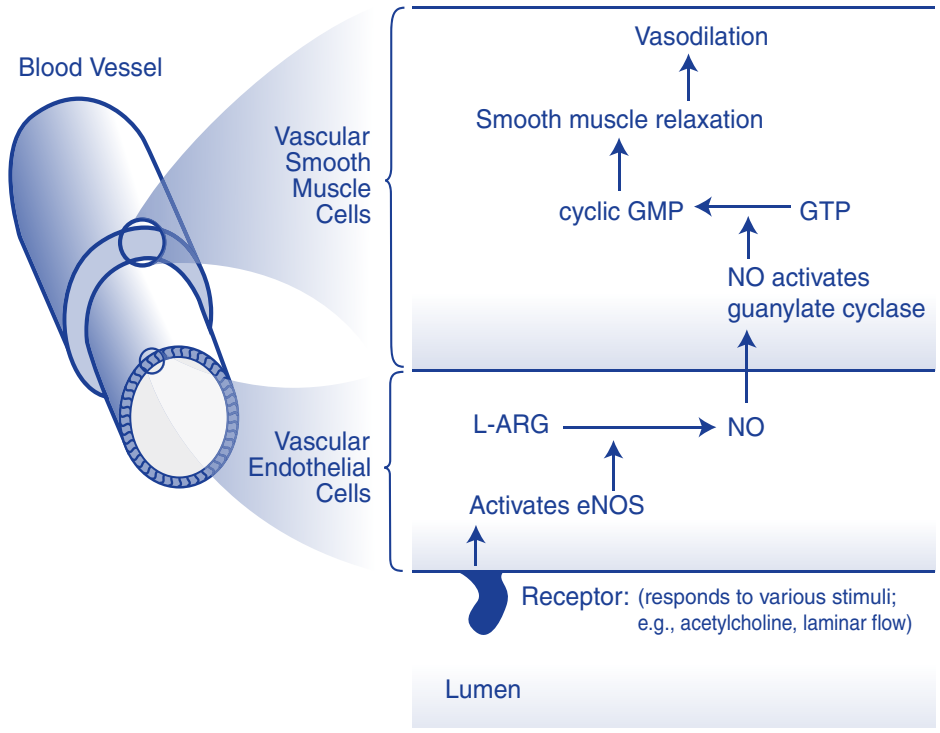
Figure 1. Nitric Oxide Synthesis and Activity in the Vasculature



Introduction

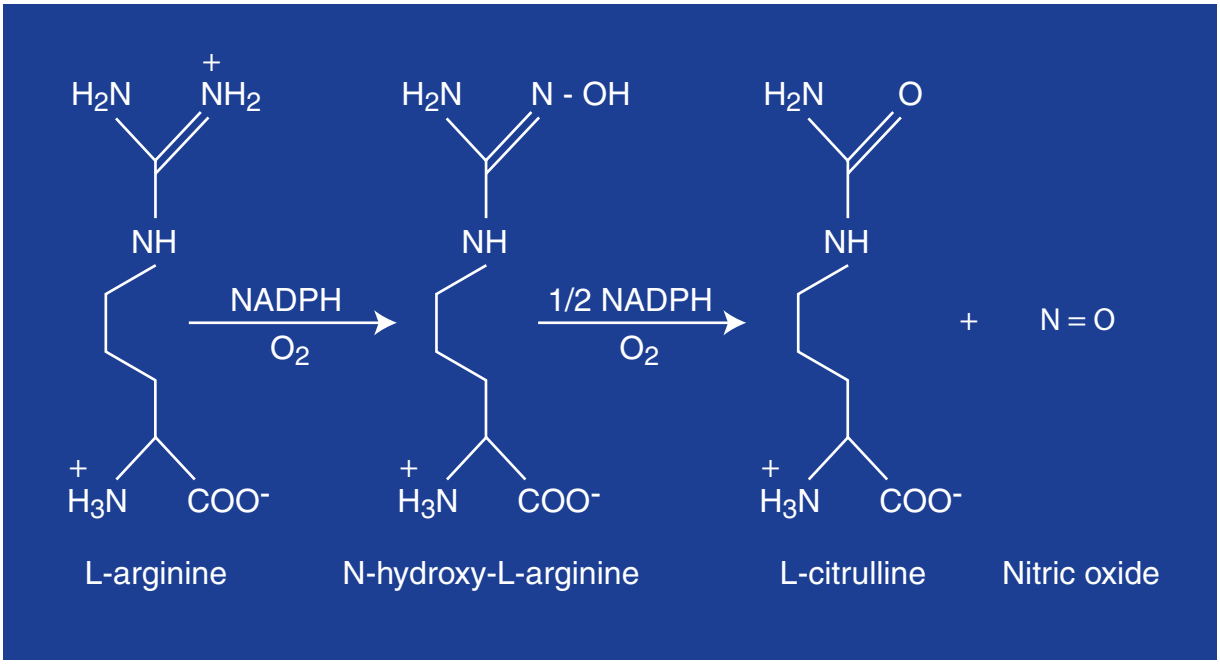
The healthy function of vascular endothelial cells is crucial to cardiovascular health. It was previously thought this single layer of cells that lines the lumen of blood vessels was merely a physical barrier between blood and the underlying tissue. However, about 20 years ago researchers began to understand that the vascular endothelium acts not only as a barrier, but also as a vital regulator of blood vessel activity, with far-reaching implications. At that time it was discovered that an endothelium-derived substance could stimulate the underlying smooth muscle to relax, thus causing vasodilation. The substance was dubbed endothelium-derived relaxing factor (EDRF). Subsequently, Robert Furchgott, Louis Ignarro, and Ferid Murad determined the identity of EDRF as nitric oxide (NO), and were honored in 1998 with the Nobel Prize in Physiology of Medicine. This discovery has resulted in thousands of papers being published on the subject of nitric oxide and endothelial function.

Nitric oxide, a simple gaseous compound consisting of one molecule of nitrogen and one molecule of oxygen, is a potent regulator of vascular function. NO is produced in vascular endothelial cells in response to a number of stimuli, including sheer stress and acetylcholine. NO diffuses into underlying vascular smooth muscle and acts as a messenger molecule, activating guanylate cyclase, which elevates the concentration of cyclic guanosine monophosphate (cGMP), which in turn causes relaxation of smooth muscle and vasodilation (Figure 1).[1]

In addition to its role in the regulation of vascular tone, NO has other significant vascular benefits. NO decreases platelet aggregation and adhesiveness, reduces monocyte adhesiveness and inflammatory cytokine release, and inhibits smooth muscle proliferation.[2] There is also evidence that adequate NO inhibits LDL oxidation.[3] These events are at the genesis of the atherosclerotic process and, without adequate nitric oxide, occur unabated. Loss of sufficient endothelial NO production appears early in the development of atherosclerosis, evidenced by impaired acetylcholine-induced vasorelaxation in hypercholesterolemic patients.[2,4] Impaired NO synthesis is a component of a number of cardiovascular conditions, including hypertension,[5-7] hyperlipidemia,[7,8] peripheral vascular disease,[9] hyperhomocysteinemia,[10,11] congestive heart failure,[12] erectile dysfunction,[13] and cerebrovascular events.[14] Poor NO production in vascular endothelial cells is also seen post balloon angioplasty.[15]

Nitric oxide is produced in vascular endothelial cells from a single natural substrate – the amino acid L-arginine. L-arginine is considered a

Figure 2. Conversion of L-Arginine to Nitric Oxide



non-essential amino acid because, in addition to being present in dietary proteins, it can be produced in the body from another amino acid, L-citrulline, in an ATP-dependent process. However, adequate dietary or supplemental L-arginine appears to be the key to sufficient NO production.

The bioconversion of L-arginine in the nitric oxide pathway results in one molecule of NO and one of L-citrulline (Figure 2). This reaction is mediated by the enzyme endothelial nitric oxide synthase (eNOS), which uses ascorbic acid and tetrahydrobiopterin as cofactors. This enzyme is inhibited by hypercholesterolemia, oxidative stress, and asymmetrical dimethylarginine (ADMA). ADMA is a methylated isomer of L-arginine derived from protein. L-arginine residues in proteins can become methylated; then the protein is hydrolyzed, releasing ADMA. ADMA is a competitive inhibitor of eNOS activity, as it binds to the L-arginine binding site on the enzyme, preventing L-arginine binding. High levels of ADMA have been positively correlated with inhibited endothelial function and an increased risk of cardiovascular disease, including acute coronary events.[16,17] It also appears the well-documented correlation between homocysteine and cardiovascular disease might be mediated by ADMA.[7] High levels of ADMA can occur due to poor liver or kidney function, and there may be a genetic component as well.[18]

Whatever the reason for elevated ADMA, increasing the L-arginine/ADMA ratio by supplementation with L-arginine overwhelms the inhibitory effect of ADMA on eNOS and subsequently improves NO production and endothelial function.[17] Research does suggest vitamin A might lower ADMA,[19] and antioxidants appear to increase the metabolism of ADMA by dehydro-dimethylarginine hydrolase (DDAH), the rate-limiting enzyme responsible for hepatic degradation of ADMA.[20] Furthermore, folic acid, vitamin B6, and vitamin B12 lower homocysteine levels, which can decrease ADMA,[21] and it is possible that ADMA levels might decrease if poor kidney or liver function is reversed.[22] However, the most reliable method of improving the L-arginine/ADMA ratio is by L-arginine supplementation.

L-arginine has been used in a number of clinical studies, achieving consistent results of improving endothelial function and blood flow. In a study at Stanford University, 43 patients with hypercholesterolemia were given 6.6 g L-arginine daily for one week. Significant improvement was noted in

Table 1. Baseline Values (n=29)

Variable	Mean ± SD
Systolic Blood Pressure (mmHg)	126.00 ± 13.95
Diastolic Blood Pressure (mmHg)	78.93 ± 10.38
EEI (large artery compliance)	0.47 ± 0.17
DDI (small artery compliance)	0.25 ± 0.09
DEI (smallest artery compliance)	0.08 ± 0.06

peripheral blood flow in the arginine-supplemented group, measured by high-resolution ultrasound of the brachial artery.[23] In a related study by the same researchers, patients with intermittent claudication experienced a 66-percent improvement in pain-free walking distance.[24] Boger et al noted even greater improvements in patients with intermittent claudication when given L-arginine intravenously. A 230-percent improvement in pain-free walking distance was seen in patients administered 8 g L-arginine twice daily for three weeks.[9]

Individuals with hypertension tend to have poor endothelial function, a condition that can be improved by L-arginine supplementation. Lekakis et al showed improved endothelial function and blood flow in hypertensive patients after a single, 6-g dose of L-arginine.[5] Palloshi et al observed improved angina and lowered blood pressure after four weeks of L-arginine supplementation (2 g, three times daily).[25] Other researchers have shown improvement with L-arginine supplementation in patients with diabetes mellitus[26] and congestive heart failure.[27,28]

A strong correlation exists between cardiovascular disease, endothelial dysfunction, and erectile dysfunction. Erectile dysfunction of an organic nature can be thought of as a red flag, indicating the need to assess and address the cardiovascular system as a whole. In a few small studies, L-arginine has been shown to benefit men with erectile dysfunction.[29,30]

Most L-arginine studies to date have used high daily doses, due to the pharmacokinetics of oral L-arginine, which reaches its highest concentration in the blood within an hour, then tapers off quickly.[31] A sustained-release L-arginine product was used in the current study.

A group of asymptomatic volunteers was recruited in order to assess the effect of seven days' dosing of a sustained-release L-arginine preparation on blood pressure and vascular compliance.

Methods

A group of volunteers was obtained from the employee population of Thorne Research, Inc., in Dover, Idaho. After completing a questionnaire, volunteers were excluded from the study if they had diagnosed liver, kidney, heart, or immune system disease. Women were disqualified from participation if pregnant or sexually active and not using birth control. Volunteers were also excluded if they were already taking an L-arginine supplement, or if they had a previous adverse reaction to an L-arginine supplement. An informed consent form was read and signed by each participant. A total of 37 asymptomatic individuals entered the study in August 2005.

Each participant's blood pressure measurement was obtained at baseline. Vascular endothelial function was assessed at baseline via digital pulse wave analysis (DPA; Meridian Medical), which is a real-time analysis of endothelial function derived from plethysmography at the left first digit. Information from the pulse wave is analyzed by a computerized mathematical algorithm and displayed as vascular compliance of the large, small, and smallest arteries. This technology has been compared to the brachial artery ultrasound technique and found to be of equal diagnostic value in assessing endothelial function.[32] See Table 1 for baseline results.

Each participant was given a one-week supply of a sustained-release L-arginine supplement (Perfusia-SR®; Thorne Research, Inc.) and instructed to take three capsules twice daily (350 mg per capsule=2.1 g daily) for seven days. Participants were instructed to continue any prescription medication, vitamin, mineral, or herbal supplement they were taking throughout the test week. After seven days, follow-up testing was performed consisting of repeat

Table 2. Change in Outcome Measures

Variable	Mean ± SD	%Change ± SD	p-value
Systolic Blood Pressure (mmHg)	-4.00 ± 12.63	-2.61 ± 9.41	0.0991
Diastolic Blood Pressure (mmHg)	-3.90 ± 6.84	-4.60 ± 8.46	0.0047
EEI (large artery compliance)	0.08 ± 0.17	22.84 ± 41.99	0.0206
DDI (small artery compliance)	0.04 ± 0.13	23.20 ± 77.67	0.1542
DEI (smallest artery compliance)	0.02 ± 0.06	14.14 ± 100.91	0.0812
Borderline or Hypertensive (n=10)			
Systolic Blood Pressure (mmHg)	-10.60 ± 14.52	-7.02 ± 9.42	0.0463
Diastolic Blood Pressure (mmHg)	-3.90 ± 6.87	-3.98 ± 7.00	0.1062
Normal Blood Pressure (n=19)			
Systolic Blood Pressure (mmHg)	-0.53 ± 10.28	-0.29 ± 8.77	0.8259
Diastolic Blood Pressure (mmHg)	-3.89 ± 7.01	-4.92 ± 9.30	0.0262

blood pressure and DPA measurements. Bottles of the supplement were brought to the follow-up visit and capsules were counted to check compliance. Three participants were not included in the data set because they did not take the supplement as directed. Two individuals dropped out due to viral upper respiratory tract illness; two did not appear for follow-up. One participant's data was dropped because he was an extreme positive outlier (725% increase in small artery compliance). A total of 29 individuals were included in the data set, including 12 females and 17 males, with an average age of 40 years; all were Caucasian.

Results

At the one-week follow-up, systolic blood pressure was reduced in 62 percent of participants, with a mean decrease in all patients of 4.0 mmHg (p=0.099). Diastolic blood pressure was reduced in 69 percent of participants, with a statistically significant mean reduction of 3.9 mmHg (p=0.005). In the 10 individuals who were borderline or hypertensive at baseline (systolic >130 or diastolic >85), a mean systolic reduction of 10.6 mmHg (p=0.05) was noted, while normotensives (n=19) had a mean decrease of 0.53 mmHg (p=0.83). Diastolic blood pressure was decreased 3.9 mmHg in borderline or hypertensives (p=0.11) and 3.9 mmHg in normotensives (p=0.026).

After one week, pulse wave analysis showed a statistically significant increase in large artery compliance (mean 23% improvement; p=0.02) and non-significant improvements in small artery compliance (mean 23% improvement; p=0.15) and smallest artery compliance (mean 14% improvement; p=0.08) (Table 2).

Discussion

This one-week study, utilizing a moderate dose of a sustained-release L-arginine formulation in 29 asymptomatic volunteers, demonstrated a statistically significant decrease in diastolic blood pressure of 3.9 points in the general study population. In the 10 individuals with borderline or frank hypertension, a highly significant reduction of 10.6 points was seen in systolic blood pressure. The reduction in systolic blood pressure in this group is on par with what is usually seen in therapeutic trials using prescription drugs, according to a recent meta-analysis of 28,436

patients in 11 clinical trials.[33] It is clinically significant because the reduction in cardiovascular risk seen with blood pressure lowering is primarily due to a reduction in systolic blood pressure in hypertensive patients.[34]

Vascular compliance, an indicator of endothelial function and perfusion, was measured by digital pulse wave analysis at baseline and at the one-week follow-up. Compliance of the large arteries was significantly improved compared to baseline. This is significant because endothelial dysfunction, which is common in many facets of cardiovascular disease (including hypertension), is associated with an increased risk of adverse cardiovascular events.[35] Improvement in vascular compliance relates to improved health and responsiveness of the blood vessels.[32,36]

Hypertensives have increased vascular tone and poor vascular response to stimuli such as acetylcholine, which is believed to be due to a decrease in nitric oxide production by the vascular endothelium.[8,37] Oral L-arginine has been shown to improve endothelial dysfunction[5] and blood pressure.[38]

Studies of sustained-release L-arginine indicate clinical efficacy at lower daily doses than many other clinical studies using non-sustained-release L-arginine. Boger et al noted improved endothelial function and increased vasodilation at the brachial artery in 12 hypercholesterolemic patients with high plasma ADMA. Patients given the HMG-CoA-reductase inhibitor simvastatin did not demonstrate improved brachial dilation. When these patients were given L-arginine (3 g sustained-release daily) a significant improvement in brachial flow-mediated dilation was noted. When given in combination, simvastatin and sustained-release L-arginine increased brachial dilation to a greater extent than L-arginine alone.[39]

Gould gave sustained-release L-arginine (6 g daily) to five patients with coronary heart disease for 12 weeks. Positron emission tomography (PET) scanning of the myocardium demonstrated significant improvements both in myocardial perfusion and in the area of the heart exhibiting 80- to 100-percent range of activity at rest. This is very clinically significant, considering these improvements in myocardial health were statistically significant even with a small number of participants.[40]

The previous clinical studies of sustained-release L-arginine used higher doses than the current study. This is the first study of sustained-release L-arginine given at the moderate dose of 1,050 mg twice daily. In 29 individuals, statistically significant, clinically relevant results – blood pressure lowering and improved endothelial functioning – were seen after one week. A larger study of longer duration is needed to show the long-term effects of dosing with this sustained-release L-arginine preparation.

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