

## L-Arginine: A Primer for Its Power

Dr. J. Joseph Prendergast

In the beginning, Dr. Robert Furchgott in 1980 found that the endothelial lining of the walls of blood vessels made a substance that kept the vessels smooth and dilated. This was Nitric Oxide (NO). Soon it was discovered that L-arginine converts to NO in the endothelium.

I learned about L-arginine in 1991 when I was in a professional association teaching physicians with Victor J. Dzau, MD when he was director of Cardiovascular Research at Stanford University Medical Center.

Dr. Dzau was appointed Chancellor for Health Affairs at Duke University and President and CEO of the Duke University Health System effective July 1, 2004. He is also James B. Duke Professor of Medicine and Director of Molecular and Genomic Vascular Biology at Duke.

Prior to that, he was the Hersey Professor of the Theory and Practice of Physic (Medicine) at Harvard Medical School, Chairman of the Department of Medicine at Brigham and Women's Hospital, and Physician-in-Chief and Director of Research at Brigham and Women's Hospital, Boston. Prior to his work at Harvard and Brigham and Women's, he served as Arthur Bloomfield Professor and Chairman of the Department of Medicine at Stanford.

He was the first to explain to me the extraordinary observation that atherosclerotic heart disease could not only be controlled but reversed. His research touched on clinical improvement and was forwarded with multiple studies by John P. Cooke, MD. Dr. Cooke is presently head of Cardiovascular Research at Stanford. Very productive on new insights and understanding of vascular health, you will find his name on many of the research papers in the following documents.

White papers, as I have labeled this, have characteristically been a document, a summary fixed in time that delivers knowledge and philosophy about some situation. This, on the other hand, is to be a living document updated continuously. It is my task to continue this project forever since it is so personal to me. I will need your help too to pass on significant information.

My personal story began with meeting these individuals. Since I had been noted to be heavily laden with atherosclerosis in my abdominal arteries at age 37 I took an uncommon interest in their research into the reversal of atherosclerosis. After 10 years of L-arginine use, I had no evidence of atherosclerosis. The testing available today with arterial wave form analysis allows me to monitor how well I'm doing with my personal regression therapy.

What other studies support this therapy?

There many studies on the effect of L-Arginine on the lining of the artery, the endothelium. The results depend on the structure of the study, the patient population and dosage of L-Arginine used. Nothing works in every situation but in my experience it works in 99% of the patients I see with vascular disease.

It does not change the endothelium in healthy people. It will change it in people who are asymptomatic but who have elevated cholesterol, hypertension or the impact of metabolism problems due to vitamin deficiencies.

Heart failure is a complex situation but the endothelial dysfunction is improved with L-Arginine. Other conditions include pulmonary hypertension, transplant vasculopathy, tobacco use, type 2 diabetes mellitus, and salt sensitive hypertension.

In patients with coronary artery disease, 2 of 4 have shown increased endothelial function, treadmill exercise time and improved symptoms. In peripheral artery disease walking distance improved 76 per cent in two of three studies. And remember, the Nobel Prize in Medicine given in 1998.

*[http://nobelprize.org/nobel\\_prizes/medicine/laureates/1998/](http://nobelprize.org/nobel_prizes/medicine/laureates/1998/)*

What is lacking is the large, double blind, placebo controlled, long term study that will answer all the questions. L-Arginine is a natural occurring product that cannot be patented. Although many pharmaceutical companies are beginning to try to develop products that have the positive aspects of L-arginine none have yet reach the market.

So far I have become the only long term study I know having started on L-arginine in 1991 when Victor Dzau introduced me to John Cooke, MD “who will tell you how much you and your patients should take”. It was my time.

In 2001 I had another CAT scan of my abdomen just like I had at age 36 that discovered my asymptomatic atherosclerosis. All my atherosclerosis was gone. I had a heart scan to confirm that all the calcium built up in the arteries was gone. None was seen. My score was zero.

The following are a few of the works that led to the time of the granting of the Nobel Prize. The subsequent published research will be from PubMed, our National Library of Medicine computerized library that is open to anyone in the world. Twice I was scheduled to speak to the United States Senate - first to be sure there would be no cut in funding and secondly to make it free to the world. I was asked to speak in favor of funding and searches being free to all based on a dramatic use of the Internet and the Library to enable a major clinical turnaround for a patient.

I did not go. The Senate did the right thing.

These will be in the summary abstracts with all the usual identification that the Library includes. These are the same features that anyone can use to find special news they may want to pursue a personal need for health information. I use it daily to stay abreast and I will use it to update this project. You should learn to use it too.

### Resources:

In the beginning...

Ignarro LJ (ed.) *Nitric Oxide: Biology and Pathobiology*, San Diego: Academic Press, 2000

Egashira K. Clinical importance of endothelial function in arteriosclerosis and ischemic heart disease. *Circ J* 2002; 66:529-533.

Hishikawa K, Nakaki T, Tsuda M, et al. Effect of systemic L-arginine administration on hemodynamic and nitric oxide release in man. *Jpn Heart J* 1992; 33:41-48

Houston M, Regan MC, The role of vascular biology, nutrition and nutraceuticals in the prevention and treatment of hypertension *JANA* 2000; Suppl 1:5-71.

What other studies support this therapy

Blum, A, et al. 2000 Oral L-arginine in patients with coronary artery disease on medical management. *Circulation* 101: 2160-64.

Boger RH, Bode-Roger SM, Thiele W, et al. Restoring vascular nitric oxide formation by L-arginine improves the symptoms of intermittent claudication in patients with peripheral arterial occlusive disease. *J Am Coll Cardiol* 1998; 32: 1336-1344.

Ceremuynski L, Chamiec T, and Herbacynska-Credo K. Effect of supplemental oral L-arginine on exercise capacity in patients with stable angina pectoris. *Am J Cardiol* 1997 80 331-33.

Clarkson P, et al. Oral L-arginine improves endothelium-dependent dilation in hypercholesterolemic young adults. *J Clin Invest* 1996 97: 1989-94.

Drexler H, et al. Correction of endothelial dysfunction in coronary microcirculation of hypercholesterolemic patient by L-arginine. *Lancet* 1991 338: 1546-50.

Lerman A, Burnett JC, Higano ST, et al. Long term L-arginine supplementation improves small vessel coronary endothelial function in humans. *Circulation* 1998; 97: 2123-2128.

Maxwell AJ, Anderson BE, Cooke JP. Nutritional therapy for peripheral arterial disease: a double-blind, placebo-controlled, randomized trial of HeartBar. *Vascular Med* 2000; 5:11-19

Siani A, Pagano E, et al. Blood pressure and metabolic changes during dietary l-arginine supplementation in humans. *Am J Hypertension* 2000; 13: 13(5Pt 1: 547-551.)

Wolf A, Zalpour CD, Theilmeyer G, et al. Dietary l-arginine supplementation normalizes platelet aggregation in hypercholesterolemic humans. *J Am Coll Cardiol* 1997, 29; 479-485.

## White Paper Clinical Trials

### Coronary Arteries

#### ***Effect of L-Arginine on Human Coronary Endothelium-Dependent and Physiologic Vasodilation***

- Quyyumi AA,
- Dakak N,
- Diodati JG,
- Gilligan DM,
- Panza JA,
- Cannon RO 3rd.

Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892-1650, USA. quyyumia@gwgate.nhlbi.nih.gov

**OBJECTIVES:** We hypothesized that L-arginine would improve abnormal coronary vasodilation in response to physiologic stress in patients with atherosclerosis and its risk factors by reversing coronary endothelial dysfunction. **BACKGROUND:** Studies have demonstrated that physiologic coronary vasodilation correlates with endothelial function and that L-arginine, the substrate for nitric oxide synthesis, improves the response to acetylcholine (Ach). **METHODS:** Changes in coronary blood flow and epicardial diameter response to Ach, adenosine and cardiac pacing were measured in 32 patients with coronary atherosclerosis or its risk factors and in 7 patients without risk factors and normal coronary angiograms. **RESULTS:** Intracoronary L-arginine did not alter baseline coronary vascular tone, but the epicardial and microvascular responses to Ach were enhanced (both  $p < 0.001$ ). The improvement after L-arginine was greater in epicardial segments that initially constricted with Ach; similarly, L-arginine abolished microvascular constriction produced by higher doses of Ach. Thus, there was a negative correlation between the initial epicardial and vascular resistance responses to Ach and the magnitude of improvement with L-arginine ( $r = -0.55$  and  $r = -0.50$ , respectively,  $p < 0.001$ ). D-Arginine did not affect the responses to Ach, and adenosine responses were unchanged with L-arginine. Cardiac pacing-induced epicardial constriction was abolished by L-arginine, but microvascular dilation remained unaffected. **CONCLUSIONS:** Thus, L-arginine improved endothelium-dependent coronary epicardial and microvascular function in patients with endothelial dysfunction. Prevention of epicardial constriction during

physiologic stress by L-arginine in patients with endothelial dysfunction may be of therapeutic value in the treatment of myocardial ischemia.

PMID: 9350919 [PubMed - indexed for MEDLINE]

1: Circulation. 1998 Jun 2;97(21):2123-8.

**Comment in:** Circulation. 1999 Mar 30;99(12):1648-9.

### ***Long-Term L-Arginine Supplementation Improves Small-Vessel Coronary Endothelial Function in Humans***

- Lerman A,
- Burnett JC Jr,
- Higano ST,
- McKinley LJ,
- Holmes DR Jr.

Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, Minn. 55905, USA.  
lerman.amir@mayo.edu

**BACKGROUND:** Coronary endothelial dysfunction is characterized by an imbalance between endothelium-derived vasodilating and vasoconstricting factors and coronary vasoconstriction in response to the endothelium-dependent vasodilator acetylcholine. Thus, the present double-blind, randomized study was designed to test the hypothesis that long-term, 6-month supplementation of L-arginine, the precursor of the endothelium-derived vasodilator NO, reverses coronary endothelial dysfunction to acetylcholine in humans with non-obstructive coronary artery disease. **METHODS AND RESULTS:** Twenty-six patients without significant coronary artery disease on coronary angiography and intravascular ultrasound were blindly randomized to either oral L-arginine or placebo, 3 g TID. Endothelium-dependent coronary blood flow reserve to acetylcholine (10(-6) to 10(-4) mol/L) was assessed at baseline and after 6 months of therapy. There was no difference between the two study groups in clinical characteristics or in the coronary blood flow in the response to acetylcholine at baseline. After 6 months, the coronary blood flow in response to acetylcholine in the subjects who were taking L-arginine increased compared with the placebo group (149 +/- 20% versus 6 +/- 9%, P < 0.05). This was associated with a decrease in plasma endothelin concentrations and an improvement in patients' symptoms scores in the L-arginine treatment group compared with the placebo group. **CONCLUSIONS:** Long-term oral L-arginine supplementation for 6 months in humans improves coronary small-vessel endothelial function in association with a significant improvement in symptoms and a decrease in plasma endothelin concentrations. This study proposes a role for L-arginine as a therapeutic option for patients with coronary endothelial dysfunction and non-obstructive coronary artery disease.

PMID: 9626172 [PubMed - indexed for MEDLINE]

1: Clin Sci (Lond). 1998 Feb;94(2):129-34.

***Lack of Effect of Vitamin E on L-Arginine-Responsive Endothelial Dysfunction in Patients with Mild Hypercholesterolaemia and Coronary Artery Disease***

- **Chowienczyk PJ,**
- **Kneale BJ,**
- **Brett SE,**
- **Paganga G,**
- **Jenkins BS,**
- **Ritter JM.**

Department of Clinical Pharmacology, UMDS, St Thomas' Hospital, London, U.K.

1. Dietary supplementation with vitamin E reduces ischaemic events in patients with established coronary artery disease and improves endothelial function in cholesterol-fed rabbits. We examined whether such dietary supplementation with vitamin E improves endothelial function in patients with mild hypercholesterolaemia and coronary artery disease. 2. Twenty patients (total cholesterol 6.8 +/- 1.1 mmol/l, mean +/- SD) with angiographically documented coronary artery disease were randomly allocated to receive placebo (n = 10) or vitamin E, 400 i.u. daily, (n = 10) for 8 weeks. Endothelium-dependent and independent vasodilatation within forearm vasculature was assessed by brachial artery infusion of acetylcholine (co-infused with saline vehicle and L-arginine) and nitroprusside before and after supplementation. 3. Plasma concentrations of vitamin E increased from 32.9 +/- 3.8 to 69.1 +/- 11.8  $\mu\text{mol/l}$  (means +/- SE) in the vitamin E-supplemented group ( $P < 0.01$ ) but did not change significantly in the placebo group. Lipid profiles remained similar before and after supplementation in both groups. Forearm blood flow responses to acetylcholine (7.5 and 15 micrograms/min) and nitroprusside (3 and 10 micrograms/min) were similar before and after supplementation in both groups. Acute intra-arterial administration of L-arginine (10 mg/min) augmented the response to acetylcholine (15 micrograms/min) in both groups before and after supplementation to a similar degree (mean augmentation: 60 +/- 18%,  $P < 0.01$ ). 4. Acute administration of L-arginine reverses endothelial dysfunction in forearm vasculature of patients with mild hypercholesterolaemia and coronary artery disease but supplementation with vitamin E (400 i.u. daily) for 8 weeks does not reverse L-arginine-responsive endothelial dysfunction.

PMID: 9536920 [PubMed - indexed for MEDLINE]

1: Am J Cardiol. 1997 Aug 1;80(3):331-3.

## ***Effect of Supplemental Oral L-Arginine on Exercise Capacity in Patients with Stable Angina Pectoris***

- Ceremuzynski L,
- Chamiec T,
- Herbaczynska-Cedro K.

Department of Cardiology, Postgraduate Medical School, and Medical Research Centre, Polish Academy of Sciences, Warsaw.

A randomized, double-blind, placebo-controlled study in patients with clinical symptoms of stable angina pectoris and healed myocardial infarction (n = 22) has shown that oral supplementation with L-arginine (6 g/day for 3 days) increases exercise capacity (tested on a Marquette case 12 treadmill according to the modified Bruce protocol). Results suggest that the inefficient L-arginine/nitric oxide system contributes to limitation of myocardial perfusion and/or peripheral vasodilation during maximum exercise in patients with stable angina pectoris.

PMID: 9264427 [PubMed - indexed for MEDLINE]

1: Am J Cardiol. 1998 Nov 1;82(9):1110-3, A6.

## ***Effects of Changing the Availability of the Substrate for Nitric Oxide Synthase by L-Arginine Administration on Coronary Vasomotor Tone in Angina Patients with Angiographically Narrowed and in Patients with Normal Coronary Arteries***

- Tousoulis D,
- Davies GJ,
- Tentolouris C,
- Crake T,
- Katsimaglis G,
- Stefanadis C,
- Toutouzas P.

Cardiology Unit, Hippokraton Hospital, Athens University Medical School, Greece.

We assessed the effects of intracoronary administration of substance P, LNMMA, L-arginine, and nitroglycerin in patients with normal coronary angiograms and in patients with coronary artery disease. LNMMA constricted ( $p < 0.01$ ) and both substance P and nitroglycerin dilated normal and diseased proximal and distal segments and stenoses ( $p < 0.01$ ). L-Arginine reversed the effect of LNMMA in all segments and caused greater dilation of the diseased arteries, including stenoses ( $p < 0.05$ ), indicating that there is a relative deficiency of L-arginine in diseased coronary arteries.

PMID: 9817490 [PubMed - indexed for MEDLINE]

***Oral L-Arginine Improves Endothelium-Dependent Dilatation and Reduces Monocyte Adhesion to Endothelial Cells in Young Men with Coronary Artery Disease***

- Adams MR,
- McCredie R,
- Jessup W,
- Robinson J,
- Sullivan D,
- Celermajer DS.

Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia.

L-Arginine is the physiological substrate for nitric oxide synthesis by the vascular endothelium. In hypercholesterolaemic rabbits, oral L-arginine reduces atheroma, improves endothelium-dependent dilatation and reduces monocyte/endothelial cell adhesion. The effect of oral L-arginine on endothelial physiology is unknown, however, in humans with established atherosclerosis. In a prospective, double-blind, randomised crossover trial, ten men aged 41 +/- 2 years with angiographically proven coronary atherosclerosis took L-arginine (7 g three times per day) or placebo for 3 days each, with a washout period of 10 days. After L-arginine, compared to placebo, plasma levels of arginine were increased (318 +/- 18 vs. 124 +/- 9  $\mu\text{mol/l}$ ,  $P < 0.01$ ) and endothelium-dependent dilatation of the brachial artery (measured as the change in diameter in response to reactive hyperaemia, using external vascular ultrasound) was improved (4.7 +/- 1.1 vs. 1.8 +/- 0.7%,  $P < 0.04$ ). No changes were seen in endothelium-independent dilatation of the brachial artery (measured as the change in diameter in response to sublingual nitroglycerine), blood pressure, heart rate or fasting lipid levels. Serum from six of the ten subjects after L-arginine and placebo was then added to confluent monolayers of human umbilical vein endothelial cells for 24 h, before human monocytes obtained by countercurrent centrifugation elutriation were added and cell adhesion assessed by light microscopy. Adhesion was reduced following L-arginine compared to placebo (42 +/- 2 vs. 50 +/- 1%,  $P < 0.01$ ). In young men with coronary artery disease, oral L-arginine improves endothelium-dependent dilatation and reduces monocyte/endothelial cell adhesion.

PMID: 9105569 [PubMed - indexed for MEDLINE]

***Oral L-Arginine Improves Endothelial Dysfunction in Patients with Essential Hypertension***

- Lekakis JP,
- Papathanassiou S,



- Papaioannou TG,
- Papamichael CM,
- Zakopoulos N,
- Kotsis V,
- Dagle AG,
- Stamatelopoulos K,
- Protogerou A,
- Stamatelopoulos SF.

Department of Clinical Therapeutics, Athens University, Alexandra Hospital, Greece. lekakisj@otenet.gr

**BACKGROUND:** L-Arginine is a nitric oxide precursor, which augments endothelium-dependent vasodilatation in hypercholesterolemic humans and animals. Endothelium-dependent vasodilation is attenuated in patients with hypertension; however the effects of oral L-arginine on endothelial function of the conduit arteries in patients with essential hypertension have not previously been investigated. **METHODS:** In a prospective randomized double blind trial, 35 patients with essential hypertension received either 6 g L-arginine (18 subjects) or placebo (17 subjects). Patients were examined for flow-mediated endothelium-dependent dilatation of the brachial artery before and 1.5 h after administration of L-arginine or placebo. At the end of the protocol the nitrate-induced, endothelium-independent vasodilatation was evaluated. **RESULTS:** Two groups of L-arginine and placebo were similar regarding age, sex, blood lipids, smoking, diabetes, coronary artery disease, body mass index, intima-media thickness of the common carotid artery, clinics blood pressure and baseline brachial artery parameters. Administration of L-arginine or placebo did not change significantly heart rate, blood pressure, baseline diameter, blood flow or reactive hyperemia. L-Arginine resulted in a significant improvement of flow-mediated dilatation (1.7+/-3.4 vs. 5.9+/-5.4%, P=0.008) while placebo did not significantly change this parameter (3.0+/-2.7 vs. 3.1+/-2.2%, P=ns). The effect of L-arginine on flow-mediated dilatation was significantly different from the effect of placebo (P=0.05). L-Arginine did not significantly influence nitrate-induced dilatation (16+/-6.9 vs. 17.7+/-6.7%, P=ns). **CONCLUSIONS:** Oral administration of L-arginine acutely improves endothelium-dependent, flow-mediated dilatation of the brachial artery in patients with essential hypertension. The long-term effects of L-arginine in these patients require further investigation.

PMID: 12419572 [PubMed - indexed for MEDLINE]

1: J Clin Invest. 1996 Apr 15;97(8):1989-94.

### ***Oral L-Arginine Improves Endothelium-Dependent Dilation in Hypercholesterolemic Young Adults***

- Clarkson P,
- Adams MR,
- Powe AJ,
- Donald AE,
- McCredie R,

- Robinson J,
- McCarthy SN,
- Keech A,
- Celermajer DS,
- Deanfield JE.

Cardiothoracic Unit, Great Ormond Street Hospital for Children NHS Trust, London, UK.

In hypercholesterolemic rabbits, oral L-arginine (the substrate for endothelium derived nitric oxide) attenuates endothelial dysfunction and atheroma formation, but the effect in hypercholesterolemic humans is unknown. Using high resolution external ultrasound, we studied arterial physiology in 27 hypercholesterolemic subjects aged 29+/-5 (19-40) years, with known endothelial dysfunction and LDL-cholesterol levels of 238+/-43 mg/dl. Each subject was studied before and after 4 wk of L-arginine (7 grams x 3/day) or placebo powder, with 4 wk washout, in a randomized double-blind crossover study. Brachial artery diameter was measured at rest, during increased flow (causing endothelium-dependent dilation, EDD) and after sublingual glyceryl trinitrate (causing endothelium-independent dilation). After oral L-arginine, plasma L-arginine levels rose from 115+/-103 to 231+/-125 micromol/liter (P<0.001), and EDD improved from 1.7+/-1.3 to 5.6+/-3.0% (P<0.001). In contrast there was no significant change in response to glyceryl trinitrate. After placebo there were no changes in endothelium-dependent or independent vascular responses. Lipid levels were unchanged after L-arginine and placebo. Dietary supplementation with L-arginine significantly improves EDD in hypercholesterolemic young adults, and this may impact favorably on the atherogenic process.

PMID: 8621785 [PubMed - indexed for MEDLINE]

1: J Am Coll Cardiol. 1997 Mar 1;29(3):491-7.

### ***Cigarette Smoking is Associated with Increased Human Monocyte Adhesion to Endothelial Cells: Reversibility with Oral L-Arginine but not Vitamin C***

- Adams MR,
- Jessup W,
- Celermajer DS.

Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia.

OBJECTIVES: This study sought to assess the effect of cigarette smoking on adhesion of human monocytes to human endothelial cells and to measure the effect of L-arginine and vitamin C supplementation on this interaction. BACKGROUND: Cigarette smoking has been associated with abnormal endothelial function and increased leukocyte adhesion to endothelium, both key early events in atherogenesis. Supplementation with both oral L-arginine (the physiologic substrate for nitric oxide) and vitamin C (an aqueous phase antioxidant) may improve endothelial function; however, their benefit in cigarette smokers is

This is third party information. This is for informational purposes only and is not intended to be used for marketing purposes.

not known. METHODS: Serum was collected from eight smokers (mean [ $\pm$ SD] age 33  $\pm$  5 years) with no other coronary risk factors and eight age- and gender-matched lifelong nonsmokers. The serum was added to confluent monolayers of human umbilical vein endothelial cells and incubated for 24 h. Human monocytes obtained by counterflow centrifugation elutriation were then added to these monolayers for 1 h, and adhesion then was measured by light microscopy. To assess reversibility, monocyte/ endothelial cell adhesion was then measured for each subject 2 h after 2 g of oral vitamin C and 2 h after 7 g of oral L-arginine. RESULTS: In smokers compared with control subjects, monocyte/ endothelial cell adhesion was increased (46.4  $\pm$  4.5% vs. 27.0  $\pm$  5.2%,  $p < 0.001$ ), endothelial expression of intercellular adhesion molecule (ICAM)-1 was increased (0.31  $\pm$  0.02 vs. 0.22  $\pm$  0.03,  $p = 0.004$ ), and vitamin C levels were reduced (33.7  $\pm$  24.1 vs. 53.4  $\pm$  11.5  $\mu$ mol/liter,  $p = 0.028$ ). After oral L-arginine, monocyte/ endothelial cell adhesion was reduced in smokers (from 46.4  $\pm$  4.5% to 35.1  $\pm$  4.0%,  $p = 0.002$ ), as was endothelial cell expression of ICAM-1 (from 0.31  $\pm$  0.02 to 0.27  $\pm$  0.01,  $p = 0.001$ ). After vitamin C, there was no significant change in monocyte/ endothelial cell adhesion or ICAM-1 expression from baseline in the smokers despite an increase in vitamin C levels (to 115  $\pm$  7  $\mu$ mol/liter). CONCLUSIONS: Cigarette smoking is associated with increased monocyte-endothelial cell adhesion when endothelial cells are exposed to serum from healthy young adults. This abnormality is acutely reversible by oral L-Arginine but not by vitamin C.

PMID: 9060883 [PubMed - indexed for MEDLINE]

1: J Am Coll Cardiol. 1995 Nov 1;26(5):1251-6.

### ***Improvement of Cardiac Performance by Intravenous Infusion of L-Arginine in Patients with Moderate Congestive Heart Failure***

- Koifman B,
- Wollman Y,
- Bogomolny N,
- Chernichowsky T,
- Finkelstein A,
- Peer G,
- Scherez J,
- Blum M,
- Laniado S,
- Iaina A, et al.

Department of Cardiology, Tel Aviv Medical Center, Tel Aviv University, Israel.

OBJECTIVES. The aim of this study was to evaluate the hemodynamic effect of L-Arginine infusion in patients with congestive heart failure. BACKGROUND. Endothelium-dependent vasodilation is impaired in patients with congestive heart failure. Nitric oxide, which was identified as endothelium-derived relaxing factor, is generated by nitric oxide synthase from L-Arginine. Our hypothesis was that administration of L-Arginine in patients with congestive

heart failure may increase nitric oxide production and have a beneficial hemodynamic effect. METHODS. Twelve patients with congestive heart failure (New York Heart Association class II or III) due to coronary artery disease (left ventricular ejection fraction < 35%) were given 20 g of L-Arginine by intravenous infusion over 1 h at a constant rate. Stroke volume, cardiac output and left ventricular ejection fraction were determined with Doppler echocardiography at baseline and at 30 and 60 min and 1 h after the end of infusion. Blood and urinary levels of nitrite/nitrate (NO<sub>2</sub>/NO<sub>3</sub>), stable metabolites of nitric oxide, were measured and clearance was calculated. RESULTS. One hour of infusion of L-Arginine resulted in a significant increase in stroke volume (from 68 +/- 18 ml to 76 +/- 23 ml [mean +/- SD], p = 0.014) and cardiac output (from 4.07 +/- 1.22 liters/min to 4.7 +/- 1.42 liters/min, p = 0.006) without a change in heart rate. Mean arterial blood pressure decreased (from 102 +/- 11 mm Hg to 89 +/- 9.5 mm Hg, p < 0.002), and systemic vascular resistance decreased significantly. Within 1 h after cessation of L-Arginine infusion, blood pressure, stroke volume, cardiac output and systemic vascular resistance were statistically not different from baseline values. Clearance of NO<sub>2</sub>/NO<sub>3</sub> increased significantly during L-arginine administration (from 13.28 +/- 0.42 ml/min to 29.97 +/- 1.09 ml/min, p < 0.001). CONCLUSIONS. Infusion of L-Arginine in patients with congestive heart failure results in increased production of nitric oxide, peripheral vasodilation and increased cardiac output, suggesting a beneficial hemodynamic and possibly therapeutic profile.

PMID: 7594039 [PubMed - indexed for MEDLINE]

1: Int J Cardiol. 2002 Dec;86(2-3):317-23.

### ***Augmented Vasodilator Response to L-Arginine After Coronary Angioplasty May Attenuate Restenosis.***

- **Fukumoto Y,**
- **Urabe Y,**
- **Kubo T,**
- **Kaku T,**
- **Egashira K,**
- **Shimokawa H,**
- **Takeshita A.**

Research Institute of Angiocardiology and Cardiovascular Clinic, Kyushu University School of Medicine, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.

Nitric oxide (NO) plays an important role in the control of vascular tone as well as structure. This study examined the possibility that the extent of restenosis 3 months after percutaneous transluminal coronary angioplasty (PTCA) might be correlated with the magnitude of NO production at the PTCA sites on the day following PTCA. In 23 consecutive patients who underwent PTCA, we examined the coronary artery diameter response to intracoronary administration of L-arginine (1 microg/kg) and isosorbide dinitrate (ISDN, 40 microg/kg) at the sites of PTCA (n = 25) and at untreated sites distal to the PTCA sites approximately 18 h

This is third party information. This is for informational purposes only and is not intended to be used for marketing purposes.

after PTCA. The coronary artery diameter at the PTCA site was determined 3 months after PTCA in all patients. Normalized vasodilator responses to L-arginine (responses to L-arginine/those to ISDN) were greater at the PTCA sites than at the untreated sites ( $P = 0.05$ ), whereas vasodilator responses to ISDN did not differ between the PTCA and untreated sites. These results suggest a greater production of NO at the PTCA sites despite presumable loss of the endothelium due to the PTCA. Furthermore, the magnitude of normalized vasodilator responses to L-arginine examined at 18 h after PTCA correlated with the coronary artery diameter 3 months after PTCA ( $r = 0.592$ ,  $P = 0.002$ ). These results suggest that augmented NO production after PTCA may protect against the development of coronary restenosis. Treatment that enhances local NO production may be clinically useful in preventing restenosis after PTCA.

PMID: 12181589 [PubMed - indexed for MEDLINE]

### ***Assessment of Endothelial Function Using Peripheral Waveform Analysis: A Clinical Application***

- **Hayward CS,**
- **Kraidly M,**
- **Webb CM,**
- **Collins P.**

Cardiology Department, St. Vincent's Hospital, Sydney, New South Wales, Australia.  
chayward@stvincents.com.au

**OBJECTIVES:** The study was done to determine whether radial artery applanation tonometry can be used as a noninvasive method of assessing global endothelial function. **BACKGROUND:** It is known that beta(2)-receptor stimulation results in endothelial release of nitric oxide. Furthermore, for over a century glyceryl trinitrate (GTN) has been known to markedly affect the arterial pressure waveform, even in the absence of significant blood pressure (BP) changes. Therefore, it was hypothesized that the change in the peripheral pressure waveform, as measured using tonometry and quantified using the augmentation index (Aix) and in response to Salbutamol (Salb), would allow assessment of global endothelial function. **METHODS:** The study contained three parts. In the first study, Salb (400 microg) was administered to 11 healthy subjects via inhalation after either intravenous N-omega-nitro-monomethyl-L-arginine (L-NMMA) (3 mg/kg over 5 min) or control solution (normal saline) in the supine, rested, fasted condition. The BP, heart rate and waveform responses were recorded each 5 min following Salb for 20 min. Next, GTN was given and responses recorded 5 min later. In the second study, both the reproducibility of Salb and the GTN responses were assessed in 9 subjects studied twice on separate days. In the third study, the Salb and GTN responses of 12 subjects with angiographic coronary artery disease (CAD) were compared with 10 age-matched control subjects with no atherosclerotic risk factors. **RESULTS:** After control infusion, Aix decreased following Salb, from 50.8 +/- 4.3% to 44.8 +/- 4.2%, a change of -11.8 +/- 3.7%,  $p < 0.01$ . After L-NMMA, Aix did not significantly change following

Salb (54.2 +/- 5.1% vs. 52.9 +/- 5.3%, -2.0 +/- 3.1%). The GTN-induced decreases in AIx were similar after either infusion (35.1 +/- 3.3% vs. 36.5 +/- 3.3%). Reproducibility of Salb-induced changes in AIx between studies performed on separate days was good ( $r = 0.80$ ,  $p < 0.01$ ). Salb-induced changes in AIx in CAD patients were significantly less compared to control subjects (-2.4 +/- 1.9% vs. -13.2 +/- 2.4%, respectively,  $p < 0.002$ ). The GTN-induced changes were not significantly different (-27.6 +/- 4.2 vs. -38.9 +/- 4.4%,  $p = 0.07$ ). CONCLUSIONS: The peripheral arterial pressure waveform is sensitive to beta(2)-stimulation. Changes are related to nitric oxide release, are reproducible and can distinguish between clinical subject groups. Arterial waveform changes following Salb may thus provide a noninvasive method of measuring "global" arterial endothelial function.

PMID: 12142121 [PubMed - indexed for MEDLINE]

1: Arterioscler Thromb Vasc Biol. 2002 Jan;22(1):147-52.

### ***Pulse-Wave Analysis: Clinical Evaluation of a Noninvasive, Widely Applicable Method for Assessing Endothelial Function***

- Wilkinson IB,
- Hall IR,
- MacCallum H,
- Mackenzie IS,
- McEniery CM,
- van der Arend BJ,
- Shu YE,
- MacKay LS,
- Webb DJ,
- Cockcroft JR.

Clinical Pharmacology Units, University of Cambridge, Addenbrooke's Hospital, Cambridge, England.  
ibw20@cam.ac.uk

Current methods for assessing vasomotor endothelial function are impractical for use in large studies. We tested the hypothesis that pulse-wave analysis (PWA) combined with provocative pharmacological testing might provide an alternative method. Radial artery waveforms were recorded and augmentation index (AIx) was calculated from derived aortic waveforms. Thirteen subjects received sublingual nitroglycerin (NTG), inhaled albuterol, or placebo. Twelve subjects received NTG, albuterol, and placebo separately during an infusion of N(G)-monomethyl-L-arginine (LN MMA) or norepinephrine. Twenty-seven hypercholesterolemic subjects and 27 controls received NTG followed by albuterol. Endothelial function was assessed by PWA and forearm blood flow in 27 subjects. Albuterol and NTG both significantly and repeatably reduced AIx ( $P < 0.001$ ). Only the response to albuterol was inhibited by LN MMA (-9.8 +/- 5.5% vs -4.7 +/- 2.7%;  $P = 0.02$ ). Baseline AIx was higher in the hypercholesterolemic subjects, who exhibited a reduced response to albuterol ( $P = 0.02$ ) but not to NTG when compared with matched controls. The responses to albuterol and

acetylcholine were correlated ( $r=0.5$ ,  $P=0.02$ ). Consistent with an endothelium-dependent effect, the response to albuterol was substantially inhibited by LNMMA. Importantly, the response to albuterol was reduced in subjects with hypercholesterolemia and was correlated to that of intra-arterial acetylcholine. This methodology provides a simple, repeatable, noninvasive means of assessing endothelial function in vivo.

PMID: 11788475 [PubMed - indexed for MEDLINE]

1: Annu Rev Pharmacol Toxicol. 2001; 41: 79-99.

### ***The Clinical Pharmacology of L-Arginine***

- **Boger RH,**
- **Bode-Boger SM.**

Institute of Clinical Pharmacology, Hannover Medical School, D-30623 Hannover, Germany.

L-Arginine (2-amino-5-guanidinovaleric acid) is the precursor of nitric oxide, an endogenous messenger molecule involved in a variety of endothelium-mediated physiological effects in the vascular system. Acute and chronic administration of L-Arginine has been shown to improve endothelial function in animal models of hypercholesterolemia and atherosclerosis. L-Arginine also improves endothelium-dependent vasodilation in humans with hypercholesterolemia and atherosclerosis. The responsiveness to L-Arginine depends on the specific cardiovascular disease studied, the vessel segment, and morphology of the artery. The pharmacokinetics of L-Arginine has recently been investigated. Side effects are rare and mostly mild and dose dependent. The mechanism of action of L-Arginine may involve nitric oxide synthase substrate provision, especially in patients with elevated levels of the endogenous NO synthase inhibitor asymmetric dimethylarginine. Endocrine effects and unspecific reactions may contribute to L-Arginine-induced vasodilation after higher doses. Several long-term studies have been performed that show that chronic oral administration of L-Arginine or intermittent infusion therapy with L-Arginine can improve clinical symptoms of cardiovascular disease in man.

PMID: 11264451 [PubMed - indexed for MEDLINE]

1: J Nutr. 2004 Oct; 134(10 Suppl): 2880S-2887S; discussion 2895S.

### ***Arginine and Endothelial and Vascular Health***

- **Gornik HL,**
- **Creager MA.**

Vascular Medicine Section, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA 02115, USA.

This is third party information. This is for informational purposes only and is not intended to be used for marketing purposes.

The vascular endothelium is a crucial regulator of vascular function and homeostasis. Nitric oxide (NO) is an important paracrine substance released by the endothelium to regulate vasomotor tone. Risk factors for atherosclerosis, as well as atherosclerosis per se, are associated with endothelial dysfunction and decreased bioavailability of NO. Indeed, endothelial dysfunction is integral to the pathogenesis of atherosclerosis and other cardiovascular diseases. Moreover, endothelial dysfunction relates to an increased risk of adverse cardiovascular outcomes. L-Arginine is an essential amino acid required by the constitutive enzyme, endothelial NO oxide synthase (eNOS), to produce NO. Administration of L-Arginine improves endothelial function in animal models and in humans with hypercholesterolemia and with atherosclerosis. Clinical trials to date support potential clinical applications of L-Arginine in the treatment of coronary artery disease and peripheral arterial disease, as well as in the prevention of in-stent restenosis. The mechanism of benefit of L-Arginine on endothelial function is unclear, because intracellular concentrations of L-Arginine far exceed that required by eNOS. One potential explanation of this "Arginine paradox" is that L-Arginine restores endothelial function in atherosclerotic patients, in whom there are elevated levels of asymmetric dimethylarginine, an endogenous inhibitor of eNOS. Given the promising findings of early studies of L-Arginine as a potential therapy for cardiovascular disorders, large-scale clinical trials are warranted.

PMID: 15465805 [PubMed - indexed for MEDLINE]

1: Curr Drug Metab. 2005 Feb;6(1):3-14.

### ***Asymmetric Dimethyl-L-Arginine (ADMA): A Possible Link Between Homocyst(e)ine and Endothelial Dysfunction***

- Stuhlinger MC,
- Stanger O.

Medical University of Innsbruck, Department of Internal Medicine, Division of Cardiology, Anichstrasse 35, A-6020 Innsbruck, Austria. Markus.Stuehlinger@uibk.ac.at

Hyperhomocyst(e)inemia is associated with an increased risk for atherosclerotic disease and venous thromboembolism. The impact of elevated plasma homocysteine levels seems to be clinically relevant, since the total cardiovascular risk of hyperhomocyst(e)inemia is comparable to the risk associated with hyperlipidemia or smoking. There is substantial evidence for impairment of endothelial function in human and animal models of atherosclerosis, occurring even before development of overt plaques. Interestingly endothelial dysfunction appears to be a sensitive indicator of the process of atherosclerotic lesion development and predicts future vascular events. NO is the most potent endogenous vasodilator known. It is released by the endothelium, and reduced NO bioavailability is responsible for impaired endothelium-dependent vasorelaxation in hyperhomocyst(e)inemia and other metabolic disorders associated with vascular disease. Substances leading to impaired endothelial function as a consequence of reduced NO generation are endogenous NO



synthase inhibitors such as ADMA. Indeed there is accumulating evidence from animal and human studies that ADMA, endothelial function and homocyst(e)ine might be closely interrelated. Specifically elevations of ADMA associated with impaired endothelium-dependent relaxation were found in chronic hyperhomocyst(e)inemia, as well as after acute elevation of plasma homocyst(e)ine following oral methionine intake. The postulated mechanisms for ADMA accumulation are increased methylation of arginine residues within proteins, as well as reduced metabolism of ADMA by the enzyme DDAH, but they still need to be confirmed to be operative in vivo. Hyperhomocyst(e)inemia, as well as subsequent endothelial dysfunction can be successfully treated by application of folate and B vitamins. Since ADMA seems to play a central role in homocyst(e)ine-induced endothelial dysfunction, another way of preventing vascular disease in patients with elevated homocyst(e)ine concentrations could be supplementation with L-arginine to reverse the detrimental effects of ADMA.

PMID: 15720202 [PubMed - indexed for MEDLINE]

1: Cardiovasc Res. 2003 Oct 1;59(4):824-33.

### ***The Emerging Role of Asymmetric Dimethylarginine as a Novel Cardiovascular Risk Factor***

- **Boger RH.**

Clinical Pharmacology Unit, Institute of Experimental and Clinical Pharmacology, Center of Experimental Medicine, University Hospital Hamburg-Eppendorf, D-20246 Hamburg, Germany. boeger@uke.uni-hamburg.de

There is abundant evidence that the endothelium plays a crucial role in the maintenance of vascular tone and structure. One of the major endothelium-derived vasoactive mediators is nitric oxide (NO). Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of NO synthase. ADMA inhibits vascular NO production at concentrations found in pathophysiological conditions (i.e., 3-15 micromol/l); ADMA also causes local vasoconstriction when it is infused intraarterially. The biochemical and physiological pathways related to ADMA are now well understood: dimethylarginines are the result of the degradation of methylated proteins; the methyl group is derived from S-adenosylmethionine. Both ADMA and its regioisomer, SDMA, are eliminated from the body by renal excretion, whereas only ADMA, but not SDMA, is metabolized via hydrolytic degradation to citrulline and dimethylamine by the enzyme dimethylarginine dimethylaminohydrolase (DDAH). DDAH activity and/or expression may therefore contribute to the pathogenesis of endothelial dysfunction in various diseases. ADMA is increased in the plasma of humans with hypercholesterolemia, atherosclerosis, hypertension, chronic renal failure, and chronic heart failure. Increased ADMA levels are associated with reduced NO synthesis as assessed by impaired endothelium-dependent vasodilation. In several prospective and cross-sectional studies, ADMA evolved as a marker of cardiovascular risk. With our increasing knowledge of the role of ADMA in the pathogenesis of cardiovascular disease, ADMA is becoming a goal for pharmacotherapeutic intervention.

This is third party information. This is for informational purposes only and is not intended to be used for marketing purposes.

Among other treatments, the administration of L-arginine has been shown to improve endothelium-dependent vascular function in subjects with high ADMA levels.

PMID: 14553822 [PubMed - indexed for MEDLINE]

1: Ann Thorac Surg. 2002 Mar; 73(3):837-41; discussion 842.

### ***Cardioplegic Arrest with L-Arginine Improves Myocardial Protection: Results of a Prospective Randomized Clinical Trial***

- Carrier M,
- Pellerin M,
- Perrault LP,
- Bouchard D,
- Page P,
- Searle N,
- Lavoie J.

Department of Surgery, Anesthesia, and Medicine, Montreal Heart Institute and the University of Montreal, Quebec, Canada. carrier@icm.umontreal.ca

**BACKGROUND:** Blood cardioplegic arrest remains the method of choice for myocardial protection. L-arginine has been suggested to improve protection through an increase in nitric oxide production. **METHODS:** A prospective, randomized, double-blinded clinical trial comparing standard blood cardioplegic solution to L-arginine-enriched solution (7.5 g/500 mL) enrolled 200 patients undergoing coronary artery bypass grafting. Clinical data and biochemical markers of ischemia were recorded. Warm blood cardioplegia (33 degrees C) was administered in 74% of patients and cold blood (20 degrees C) was used in 26% of patients. Both groups averaged three grafts per patient. **RESULTS:** There were two (2%) deaths in both groups. There were four (4%) myocardial infarctions (MI) in the control group and six (6%) infarctions in the L-arginine group ( $p = 0.5$ ). For the 190 patients without MI, serum levels of troponin T averaged  $0.40 \pm 0.43$ ,  $0.38 \pm 0.42$ , and  $0.39 \pm 0.50$  microg/L in control patients compared with  $0.28 \pm 0.22$ ,  $0.24 \pm 0.18$ , and  $0.27 \pm 0.20$  microg/L in L-arginine patients, respectively, 12, 24 and 48 hours after coronary artery bypass grafting ( $p = 0.03$ ). The cardiac index averaged  $2.7 \pm 0.8$  L x min<sup>(-1)</sup> x m<sup>(-2)</sup> in control patients and  $2.9 \pm 0.7$  L x min<sup>(-1)</sup> x m<sup>(-2)</sup> in arginine patients immediately after surgery ( $p = 0.09$ ). Intensive care unit and hospital length of stay averaged  $3.5 \pm 5$  days and  $7.3 \pm 6$  days in control patients compared with  $2.5 \pm 3$  days and  $6.1 \pm 4$  days in arginine patients ( $p = 0.09$ ). **CONCLUSIONS:** L-arginine-supplemented blood cardioplegic solution is associated with reduced release of biochemical markers of myocardial damage, suggesting improved myocardial protection.

PMID: 11899188 [PubMed - indexed for MEDLINE]

## ***L-Arginine Effects on Myocardial Stress in Cardiac Surgery: Preliminary Results***

- **Colagrande L,**
- **Formica F,**
- **Porta F,**
- **Brustia M,**
- **Avalli L,**
- **Sangalli F,**
- **Muratore M,**
- **Paolini G.**

Surgical Science and Intensive Care Department, Cardiac Surgery Clinic, University of Milan-Bicocca, San Gerardo Hospital, Monza, Italy. Icolagrande@yahoo.it

**BACKGROUND:** L-arginine in addition to cardioplegia stimulates the release of nitric oxide and increases coronary blood flow, decreasing platelet activation and leukocyte adhesion. The aim of our study was to determine the feasibility and the efficacy of the addition of L-arginine to antegrade and retrograde blood cardioplegia in reducing myocardial damage and stress.

**METHODS:** Twenty-eight consecutive patients who underwent coronary artery bypass grafting were randomized to receive 7.5 g of L-arginine in 500 ml of cardioplegic solution. To assess safety of use of L-arginine, hemodynamic evaluation was performed before sternum opening, at sternum closure, and 1 hour after arrival in the intensive care unit to measure cardiac index, systemic and pulmonary vascular resistances, and pulmonary capillary wedge pressure. Moreover, transesophageal echocardiography was performed to assess myocardial contractility. To determine the effects on myocardial stress, blood samples were taken from the retrograde coronary sinus catheter for lactate, interleukin (IL)-2 receptor, IL-6 and tumor necrosis factor (TNF)-alpha levels. Serum samples (preoperatively, 2, 18 and 42 hours after aortic cross-clamping removal) were also analyzed to measure creatine phosphokinase, creatine kinase-MB mass, cardiac troponin T, platelets, and leukocytes. **RESULTS:** We found statistical differences for IL-2 receptor, IL-6, TNF-alpha, platelets and leukocytes, in favor of the treated group, and decreasing trends in creatine kinase-MB mass and troponin T levels. **CONCLUSIONS:** The present study shows the positive effects of the addition of L-arginine to cardioplegia. Reduced IL-2 receptor, IL-6 and TNF-alpha indicate a decrease in myocardial stress. Safety of L-arginine is related to lower values of systemic vascular resistances and pulmonary capillary wedge pressure observed in group A postoperatively that could improve the patient's outcome in terms of a reduced need for inotropic support. Moreover, the decrease in platelet and leukocyte count in the treated group might express a reduced no-reflow phenomenon and a better reperfusion, limiting endothelial injury from oxygen radical production.

PMID: 16320926 [PubMed - indexed for MEDLINE]

1: Am J Cardiol. 2002 Feb 15;89(4):363-7.

## ***Effect of Local Delivery of L-Arginine on In-Stent Restenosis in Humans***

- Suzuki T,
- Hayase M,
- Hibi K,
- Hosokawa H,
- Yokoya K,
- Fitzgerald PJ,
- Yock PG,
- Cooke JP,
- Suzuki T,
- Yeung AC.

Division of Cardiovascular Medicine, Stanford University, Stanford, California 94305, USA.

To determine whether intramural administration of L-arginine reduces intimal thickening after optimal Palmaz-Schatz stent deployment in humans, 50 patients with native coronary artery disease who received a single Palmaz-Schatz stent were enrolled in this pilot study. Patients were randomized into 2 treatment groups: an L-arginine group (n = 25) and a saline group (n = 25). After stent deployment, L-arginine (600 mg/6 ml) or saline (6 ml) was locally delivered via the Dispatch catheter (Scimed) over 15 minutes. Serial angiography and intravascular ultrasound examinations (motorized pull-back at 0.5 mm/s) were performed before and after the procedure, and at 6-month follow-up. Measurements of stent area, lumen area, and neointimal area were computed within the stents at 1-mm intervals, by technicians who were blinded to the treatment assignment. Using Simpson's rule, stent, plaque, and lumen volumes, neointimal volume within the stent, and percent neointimal volume were measured before and after the procedure, and at 6-month follow-up. The 6-month volume data in quantitative coronary ultrasound showed that neointimal volume in the L-arginine group was significantly less than in the saline group (25 vs 39 mm<sup>3</sup>; p = 0.049). Similarly, percent neointimal volume was significantly less in the L-arginine group at 6-month follow-up (17 +/- 13% vs 27 +/- 21%; p = 0.048). Thus, these results showed that local delivery of L-arginine reduces in-stent neointimal hyperplasia in humans, indicating that this approach may be a novel strategy to prevent in-stent restenosis.

PMID: 11835911 [PubMed - indexed for MEDLINE]

1: Expert Opin Pharmacother. 2001 Nov;2(11):1765-75.

## ***Pharmacological Approaches to Preserving and Restoring Coronary Endothelial Function***

- Woodman OL.

Department of Pharmacology, University of Melbourne, Victoria, 3010, Australia.  
owenlw@unimelb.edu.au

There is compelling evidence that the endothelium is critical to normal coronary vascular function and that endothelial dysfunction, generally indicated by an impairment of endothelium-dependent vasodilatation, is an important component of coronary artery disease (CAD). Endothelial cells synthesise and release a number of factors, including prostacyclin, nitric oxide (NO), endothelium-derived hyperpolarising factor (EDHF) and endothelin, which are important in the regulation of vascular tone and the control of platelet and leukocyte adhesion, aggregation and migration. NO appears to be the critical factor in the preservation of normal coronary vascular function and there is a well-established correlation between CAD and an impairment of NO activity. Thus, to preserve endothelial function, drugs have been used to either increase the synthesis of NO, or to decrease its breakdown. Fortuitously, compounds such as the HMG-CoA reductase inhibitors, angiotensin (AT) converting enzyme inhibitors (ACEIs), AT receptor antagonists and oestrogen, which have been introduced into clinical practice because of other beneficial effects, have also been shown to improve coronary endothelial function through a variety of mechanisms. In addition, L -arginine, the substrate for NO synthesis, and the anti-oxidants ascorbate and alpha-tocopherol, are able to increase NO synthesis and bioavailability respectively. Studies in experimental animals strongly support the ability of these agents to enhance the activity of endothelium-derived NO but clinical trials have failed to demonstrate reversal of established CAD. Whether these agents preserve endothelial function and prevent the development of CAD remains to be established.

PMID: 11825315 [PubMed - indexed for MEDLINE]

1: Clin Nutr. 2005 Dec;24(6):988-97. Epub 2005 Sep 6.

### ***L-Arginine Improves Endothelial Function and Reduces LDL Oxidation in Patients with Stable Coronary Artery Disease***

- Yin WH,
- Chen JW,
- Tsai C,
- Chiang MC,
- Young MS,
- Lin SJ.

Division of Cardiology, Cheng-Hsin General Hospital, and Institute of Clinical Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan.

**BACKGROUND:** We investigated the effects of oral L-Arginine on endothelial function, intravascular oxidative stress, and circulating inflammatory markers in patients with stable coronary artery disease (CAD). **METHODS:** Thirty-one stable CAD patients were randomly assigned to oral L-Arginine (10 g) or vitamin C (500 mg, an antioxidant, as active control) daily for 4 weeks, with crossover to the alternate therapy after 2 weeks off therapy, in this study. Brachial artery endothelial function studies were performed and serum concentrations of lipids and inflammatory markers were measured at baseline, at the end of each 4-week treatment period and at the 2-week wash-out period. Susceptibility of low-density lipoprotein

This is third party information. This is for informational purposes only and is not intended to be used for marketing purposes.

(LDL) particles to oxidation, a marker of oxidative stress, was determined in 11 patients at random before and after 4-week treatment of oral L-arginine. RESULTS: We demonstrates that consumption of either L-arginine or vitamin C significantly increased brachial artery flow-mediated dilatation (mean diameter change from baseline of 4.87%,  $P < 0.0001$  and of 3.17%,  $P = 0.0003$ , respectively). Neither oral L-arginine nor vitamin C affected lipid profiles and circulating levels of inflammatory markers. However, in the 11 patients whose LDL susceptibility to oxidation was determined, lag time significantly increased by 27.1% ( $P = 0.045$ ) after consumption of L-arginine for 4 weeks. CONCLUSIONS: Oral L-Arginine supplement improved endothelial function and reduced LDL oxidation in stable CAD patients.

PMID: 16140428 [PubMed - indexed for MEDLINE]

1: Am J Cardiol. 2004 Sep 15;94(6):828-31.

### ***Effect of Oral L-Arginine on Oxidant Stress, Endothelial Dysfunction, and Systemic Arterial Pressure in Young Cardiac Transplant Recipients***

- Lim DS,
- Mooradian SJ,
- Goldberg CS,
- Gomez C,
- Crowley DC,
- Rocchini AP,
- Charpie JR.

Department of Pediatrics, University of Virginia, Charlottesville, VA 22908-0386, USA.  
SL9PC@virginia.edu

Oral L-Arginine therapy reverses endothelial dysfunction and attenuates high blood pressure in hypertensive cardiac transplant recipients. L-Arginine corrects derangements in the vascular endothelial nitric oxide (NO)-dependent signaling pathway. Our data support the concept that cardiac transplant recipients use excess endogenous NO from L-Arginine supplementation to buffer increased vascular oxidant stress.

PMID: 15374803 [PubMed - indexed for MEDLINE]

**Comment in:** Circulation. 1999 Mar 30;99(12):1648-9.

### ***Long-Term L-Arginine Supplementation Improves Small-Vessel Coronary Endothelial Function in Humans***

- Lerman A,
- Burnett JC Jr,
- Higano ST,

- McKinley LJ,
- Holmes DR Jr.

Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, Minn. 55905, USA.  
lerman.amir@mayo.edu

**BACKGROUND:** Coronary endothelial dysfunction is characterized by an imbalance between endothelium-derived vasodilating and vasoconstricting factors and coronary vasoconstriction in response to the endothelium-dependent vasodilator acetylcholine. Thus, the present double-blind, randomized study was designed to test the hypothesis that long-term, 6-month supplementation of L-arginine, the precursor of the endothelium-derived vasodilator NO, reverses coronary endothelial dysfunction to acetylcholine in humans with nonobstructive coronary artery disease. **METHODS AND RESULTS:** Twenty-six patients without significant coronary artery disease on coronary angiography and intravascular ultrasound were blindly randomized to either oral L-arginine or placebo, 3 g TID. Endothelium-dependent coronary blood flow reserve to acetylcholine (10(-6) to 10(-4) mol/L) was assessed at baseline and after 6 months of therapy. There was no difference between the two study groups in clinical characteristics or in the coronary blood flow in the response to acetylcholine at baseline. After 6 months, the coronary blood flow in response to acetylcholine in the subjects who were taking L-arginine increased compared with the placebo group (149 +/- 20% versus 6 +/- 9%, P < 0.05). This was associated with a decrease in plasma endothelin concentrations and an improvement in patients' symptoms scores in the L-arginine treatment group compared with the placebo group. **CONCLUSIONS:** Long-term oral L-arginine supplementation for 6 months in humans improves coronary small-vessel endothelial function in association with a significant improvement in symptoms and a decrease in plasma endothelin concentrations. This study proposes a role for L-arginine as a therapeutic option for patients with coronary endothelial dysfunction and nonobstructive coronary artery disease.

PMID: 9626172 [PubMed - indexed for MEDLINE]

1: J Thorac Cardiovasc Surg. 2005 Jun;129(6):1414-20

***Normalization of Coronary Microvascular Reactivity and Improvement in Myocardial Perfusion by Surgical Vascular Endothelial Growth Factor Therapy Combined with Oral Supplementation of L-Arginine in a Porcine Model of Endothelial Dysfunction***

- Voisine P,
- Bianchi C,
- Khan TA,
- Ruel M,
- Xu SH,
- Feng J,
- Li J,
- Malik T,

- Rosinberg A,
- Sellke FW.

Division of Cardiothoracic Surgery, Beth Israel Deaconess Medical Center, Boston, Mass, USA.

**OBJECTIVE:** Vascular endothelial growth factor acts in part through nitric oxide release, the availability of which is decreased in endothelial dysfunction associated with advanced coronary artery disease. This could explain the relatively disappointing results of vascular endothelial growth factor therapy in clinical studies compared with animal studies. We examined the influence of L-arginine supplementation to vascular endothelial growth factor therapy on myocardial microvascular reactivity and perfusion in a porcine model of endothelial dysfunction. **METHODS:** Twenty-four pigs were fed either a normal (NORM, n = 8) or high-cholesterol diet with (CHOL-ARG, n = 8) or without (CHOL, n = 8) L-arginine. All pigs underwent ameroid placement on the circumflex artery and then 3 weeks later received surgical vascular endothelial growth factor treatment. Four weeks after treatment, endothelial-dependent coronary microvascular responses and lateral myocardial perfusion were assessed. Endothelial cell density was determined by means of immunohistochemistry. Vascular endothelial growth factor, endothelial nitric oxide synthase, and Akt levels were determined by means of immunoblotting. **RESULTS:** Pigs from the CHOL group showed endothelial dysfunction in the circumflex territory, which was normalized by L-arginine supplementation. Vascular endothelial growth factor treatment was ineffective in the CHOL group (circumflex/left anterior descending coronary artery blood flow ratios: 0.95 [rest] and 0.74 [pace] before-after treatment; P < .05 compared with the NORM group). Addition of L-arginine restored the angiogenic effect of vascular endothelial growth factor (ratios: 1.13 [rest] and 1.20 [pace]; P < .05) and was associated with increased endothelial cell density, as well as vascular endothelial growth factor, endothelial nitric oxide synthase, and Akt protein levels in the ischemic territory. **CONCLUSIONS:** L-Arginine supplementation can restore normal endothelium-dependent vasorelaxation and angiogenic response to vascular endothelial growth factor in a swine model of chronic myocardial ischemia with hypercholesterolemia-induced endothelial dysfunction. These findings suggest a putative role for L-arginine in combination with vascular endothelial growth factor therapy for end-stage coronary artery disease.

PMID: 15942586 [PubMed - indexed for MEDLINE]

1: Am J Cardiol. 2004 Apr 1;93(7):933-5.

***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***

- Palloshi A,
- Fragasso G,
- Piatti P,
- Monti LD,

This is third party information. This is for informational purposes only and is not intended to be used for marketing purposes.



- **Setola E,**
- **Valsecchi G,**
- **Galluccio E,**
- **Chierchia SL,**
- **Margonato A.**

Division of Clinical Cardiology, Istituto Scientifico San Raffaele, Milan, Italy. altin\_p@hotmail.com

Thirteen hypertensive patients with microvascular angina were studied before and after receiving oral L-Arginine (4 weeks, 2 g, 3 times daily). L-arginine significantly improved angina class, systolic blood pressure at rest, and quality of life. Maximal forearm blood flow, plasma L-arginine, L-Arginine:asymmetric dimethyl Arginine ratio, and cyclic guanylate monophosphate increased significantly after treatment. In medically treated hypertensive patients with micro-vascular angina, oral L-arginine may represent a useful therapeutic option.

PMID: 15050504 [PubMed - indexed for MEDLINE]

1: Cardiovasc Res. 1998 Nov; 40(2):410-7.

### ***Syndrome X and Endothelial Dysfunction***

- **Bellamy MF,**
- **Goodfellow J,**
- **Tweddel AC,**
- **Dunstan FD,**
- **Lewis MJ,**
- **Henderson AH.**

Department of Cardiology, University of Wales College of Medicine, Cardiff, UK.

**OBJECTIVE:** Syndrome X (angina, normal coronary arteriogram and positive exercise test) remains an enigma with unexplained features and apparent conflicts of evidence. The present study addressed whether (i) the Syndrome is characterized by generalized flow-related endothelial dysfunction, (ii) myocardial thallium201 defects reflect myocardial or microvascular dysfunction, (iii) endothelial dysfunction and its consequences can be improved by oral L-arginine. **METHODS:** Flow-mediated brachial artery dilatation was measured by ultrasonic 'wall-tracking' in 7 Syndrome X patients, further characterized as having thallium201 defects and no known cause of endothelial dysfunction, and a normal control group. Syndrome X patients entered a 4-week randomized double-blind placebo-controlled cross-over trial of oral L-arginine (7 g twice daily), with brachial artery studies, exercise tests and technetium99 tetrafosmin scans. **RESULTS:** Flow-mediated dilatation was absent in Syndrome X vs. normal. Stress technetium99 tetrafosmin and thallium201 scans showed similar defects. Flow-mediated dilatation, symptom-limited exercise duration and peak oxygen consumption (VO<sub>2</sub>max) were increased but rate-pressure-product (RPP) and radionuclide defects were unchanged after L-arginine vs. placebo. **CONCLUSIONS:** The study supports

This is third party information. This is for informational purposes only and is not intended to be used for marketing purposes.

coronary microvascular rather than myocardial dysfunction and shows loss of flow-mediated dilatation in systemic arteries. Oral L-arginine improved flow-mediated dilatation, exercise capacity and VO<sub>2</sub>max (by ca. 17%) despite unchanged RPP. The findings support generalized endothelial dysfunction. The arginine effects imply NO-mediated improvement of skeletal muscle perfusion suggesting improved homogeneity of microvascular distribution.

PMID: 9893736 [PubMed - indexed for MEDLINE]

1: Cardiovasc Res. 1998 Nov; 40(2):410-7.

*About the author: Dr. J. Joseph Prendergast is an endocrinologist that specializes in the treatment of diabetes. He has published more than 40 papers and his recent book, The Uncommon Doctor. He serves on numerous boards, including the California Medical Review Board and he recently received an award from the American Medical Association for his humanitarian efforts. Dr. Prendergast has lectured extensively in the United States is considered to be one of the foremost thought leaders in his field.*