

# **L-Arginine Improves Vascular Endothelial Function – A Key Component of Cardiovascular Health**

**by Douglas MacKay, ND**

Elevated cholesterol is widely accepted as an independent risk factor for cardiovascular disease. However, with the near-hysteria surrounding high cholesterol and its treatment over the past 30 years, a few important pieces of the cardiovascular health puzzle have been ignored. One important aspect lies in the health of the inner layer of cells lining all blood vessels – the vascular endothelial cells. This is important because, if a cholesterol-laden plaque is going to form, there must first be a breakdown of the normal protective mechanisms in these cells. And what is the key to these protective mechanisms? L-arginine, an amino acid found in proteins. More specifically, the nitric oxide (NO) produced from L-arginine in the vascular endothelial cells protects these important cells.

The amino acid L-arginine is vital to vascular health because it is the only naturally occurring substance in the body that produces NO. NO is a simple molecule – a gas composed of one atom of nitrogen and one atom of oxygen produced in the body from the conversion of L-arginine to L-citrulline. The NO molecule produced in this reaction is short-lived. It diffuses from the vascular endothelium (the one-cell-thick lining of the inside of blood vessels) into the underlying smooth muscle that surrounds arteries. In the smooth muscle cell, NO turns on cyclic GMP, a messenger molecule that signals the smooth muscle to relax, causing vasodilation. This happens very quickly, so arteries can respond to situations that require increased blood flow almost immediately. The bottom line: increased blood flow.

Information about NO's activity in the body is fairly new, in scientific terms. Researchers in the 1980s and 1990s knew a substance produced by vascular endothelial cells caused relaxation of the underlying smooth muscle and subsequently increased blood perfusion to distal tissues, but it took time to identify the substance. Three researchers and their teams ultimately described this "endothelium-derived relaxing factor" as NO. This discovery led to the presentation of the 1998 Nobel Prize in Physiology or Medicine to Robert Furchgott, Louis Ignarro, and Ferid Murad. Since their discovery, tens of thousands of research papers about NO and its effects on the vascular endothelium have been published.

Improved blood flow is not the only effect of L-arginine and NO. Nitric oxide creates a health-promoting environment in the vascular endothelium by making these cells more resistant to damage by oxidative forces. NO also helps prevent adhesion of white blood cells (monocytes) to the endothelium, which is one of the first steps in the process of atherosclerosis. Another way NO can prevent atherosclerosis is by inhibiting platelet aggregation and adhesion to the vessel wall, which prevents the formation of blood clots, a cause of heart attack and stroke. NO also inhibits atherosclerosis-promoting inflammation in blood vessels.

Unfortunately, if inadequate NO exists, endothelial cells can be damaged by oxidation and the atherosclerotic process, and the endothelium is further unable to produce NO, creating a vicious cycle. Numerous scientific studies have shown a deficiency in NO production reduces blood flow, increases blood pressure, and increases the risk of atherosclerosis and its resultant effects, including heart attack, stroke, peripheral vascular disease, and erectile dysfunction.

Since L-arginine is the only natural substrate for NO production in the body, supplementation of L-arginine can be

beneficial to anyone with cardiovascular health issues, as it promotes improved blood flow, reduced blood pressure, and increased fluidity of the blood.

L-arginine is not considered to be an essential amino acid because it is manufactured in the body from L-citrulline. However, if there is inadequate dietary protein intake, inadequate conversion from L-citrulline, poor liver or kidney function, or specific genetically-induced enzyme problems, the body needs supplemental L-arginine. A number of studies have shown that poor endothelial function increases the risk of cardiovascular disease, and supplemental L-arginine can improve endothelial function and reduce these risks.

One of the premier L-arginine and NO researchers in the United States is Dr. John Cooke, at Stanford University. In one study, his research group gave 43 patients with increased cholesterol levels a food bar that provided 6.6 grams of L-arginine daily. After one week, a significant improvement in peripheral blood flow was seen in the arginine-supplemented group, compared to another group who ate a placebo bar (one not containing L-arginine). Dr. Cooke's researchers also studied patients with the peripheral vascular disease called intermittent claudication. After two weeks of treatment with the L-arginine-containing bar, patients could walk 66% farther before feeling pain in the legs. No improvement took place in the placebo group.

Dr. Rainer Boger, of the University of Hamburg, Germany, is a worldwide expert in L-arginine and NO research. He is a prolific researcher who has published dozens of papers on NO and arginine. Dr. Boger found improvements in intermittent claudication, with a 230% improvement in pain-free walking distance in patients taking high-dose L-arginine (8 grams twice daily).

The cardiovascular effects of L-arginine are not limited to intermittent

claudication. Researchers in Greece found that individuals with hypertension have poor endothelial function and showed improved endothelial function and blood flow after one dose of L-arginine (six grams). An Italian research group observed improved angina and lowered blood pressure after four weeks on L-arginine (two grams, three times daily). Other researchers have seen improvement in patients with diabetes mellitus and congestive heart failure.

Another effect of L-arginine that can have a profound impact on quality of life in men is its effect on achieving erections. The mechanism of erections involves relaxation of vascular smooth muscle in the penis, with subsequent engorgement. This mechanism is exactly where L-arginine has its effect. In fact, some studies estimate that an extremely strong crossover exists between cardiovascular disease and erectile dysfunction (ED). L-arginine has been shown in a few studies to benefit men with ED. One study found a synergistic effect between sildenafil (Viagra™) and L-arginine. Patients taking both could take a smaller amount of Viagra when they also took arginine, and obtain the same results. This could be an opportunity for middle-aged men with varying degrees of ED to improve erections, while benefiting the entire cardiovascular system. This effect also improves compliance, as men can take L-arginine on a daily basis and be able to respond to sexual stimuli as needed, without having to plan ahead for their dose of Viagra or similar drug. There are anecdotal reports of L-arginine increasing sexual response in women, which makes sense, but no studies have been done as yet.

Most of the L-arginine studies to date have used high daily doses. This is probably because that L-arginine taken orally reaches its highest concentration in the blood within an hour, then tapers off quickly. So, to achieve high enough blood levels over time, one must take large doses, or



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▶ smaller doses frequently throughout the day. A sustained-release L-arginine product (Perfusia-SR™, Thorne Research, Inc.) is available that appears to solve this dilemma. Perfusia-SR releases its L-arginine slowly over 10-12 hours, with peak blood concentrations being delayed significantly. This makes lower doses taken just twice daily very easy for the patient.

Many people with high blood cholesterol take a cholesterol-lowering "statin" drug daily (e.g., Simvastatin, Lovastatin, Pravastatin, etc.). These drugs usually lower cholesterol significantly, but do not always improve the function and health of vascular endothelial cells. Dr. Boger, in Hamburg, Germany, performed a study on the effect of Perfusia-SR, taken by itself and along with a statin drug, on forearm blood flow (an indirect measurement of vascular endothelial function) in people with high cholesterol. These people also had high blood levels of a substance called asymmetric dimethylarginine (ADMA), which looks enough like L-arginine that it fools the endothelium into absorbing it. But ADMA blocks the conversion of L-arginine to NO by the enzyme endothelial nitric oxide synthase (eNOS). So, high ADMA means low NO. And low NO means less blood flow and increased risk of cardiovascular disease.

After three weeks' dosing of Perfusia-SR at 1.5 grams twice daily, volunteers had significantly improved blood flow. The statin drug (simvastatin) did not cause an improvement in blood flow. But, when individuals took Perfusia-SR and simvastatin together they got even better blood flow. So, Perfusia-SR "unlocked" the potential for the statin drug to improve blood flow. Since so many people are on statins, this is an important breakthrough. The addition of L-arginine as the sustained-release Perfusia-SR to a cholesterol-lowering

statin regimen offers significantly more benefit to the patient than the statin drug alone.

Dr. K. Lance Gould, at the University of Texas in Houston, performed a pilot study using Perfusia-SR in five patients with significantly reduced blood flow to the myocardial heart muscle. Dr. Gould gave patients 3 grams sustained-release L-arginine (Perfusia-SR) twice daily for 12 weeks. Using positron emission tomography (PET scanning), he found a statistically significant improvement in myocardial blood flow and a 22% improvement in heart muscle function.

At Thorne Research, in Dover, Idaho, Dr. Alan Miller studied 29 volunteers with no known cardiovascular disease. Blood pressure and digital pulse wave analysis (Meridian Medical, Vancouver, British Columbia) – a measurement of vascular endothelial function – were tested at baseline. Each participant took three capsules (1,050 mg) of Perfusia-SR twice daily for seven days, and were then re-tested. After one week, there was a significant drop of four points in the diastolic blood pressure. Individuals, who had borderline or frank hypertension, experienced a significant 11-point drop in systolic blood pressure. A statistically significant 22% improvement in large blood vessel elasticity on digital pulse wave analysis (greater elasticity equals better blood vessel dilation and better blood flow) also appeared. These are impressive results when you consider this was after only one week and at a lower dose than many L-arginine clinical studies.

## Recommendations

The recommended dose of Perfusia-SR is three capsules twice daily. I have noticed that some patients can lower the dose after about one month to two capsules twice daily. It does not matter if it is taken with meals or between meals.

Some people with Herpes simplex who take L-arginine by itself have an increased incidence of Herpes outbreaks. If the patient has a history of herpes, make sure to give 500-1000 mg L-lysine daily.

A few studies on hepatocellular carcinoma note that this particular cancer might prefer L-arginine for growth. It is not recommended that individuals with hepatocellular carcinoma take supplemental arginine.

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