

Letter to the Editor re: JAMA Article on L-Arginine Therapy in Acute Myocardial Infarction

Editors,

In the January 4, 2006, issue of the *Journal of the American Medical Association*, Schulman and colleagues reported on their six-month study of 153 patients who had very recently experienced a myocardial infarction. These individuals were given up to 9 grams L-arginine daily or a placebo. Outcome measurements included plasma L-arginine, vascular elasticity, and acute cardiac events. The study was discontinued at six months due to the deaths of six individuals in the L-arginine group, compared to none in the placebo group.

The researchers deserve respect for their article¹ for putting the dietary supplement L-arginine under the same rules for proof of efficacy as any medical therapy. However, their results, including an observed lack of change in measures of vascular stiffness as compared to placebo, require some comment.

There was no difference in L-arginine plasma levels between the two treatment groups, nor was there a dose-related difference in L-arginine plasma levels, at six months.¹ The study used standard L-arginine dietary supplements, for which we previously determined the plasma half-life to be about one hour.² Thus, there was little chance to induce a sustained elevation of L-arginine plasma levels in morning blood samples after evening dosing in this study. This lack of sustained elevation of L-arginine plasma levels is a reasonable cause for the lack of clinical effectiveness of the dietary intervention. Therefore, sustained-release L-arginine may be a better-suited alternative to provide sustained elevation of L-arginine plasma levels around the clock.³

In correspondence with the data by Schulman et al,¹ we found no improvement in endothelium-dependent vasodilation after two weeks of L-arginine ingestion (5 g tid) in patients with stable coronary artery disease (CAD),⁴ and Blum et al similarly found no improvement in vascular function after one month of L-arginine supplementation (9 g/d) in 30 CAD patients.⁵ All of these patients were maximally treated with standard postinfarction medical therapy before the initiation of L-arginine supplements. There may have been little room for improvement in this setting, leading to negative study results. Moreover, patients with poor NO synthase activity are more likely to benefit from L-arginine supplementation. These patients can be identified by screening for elevated levels of the endogenous inhibitor of

NO synthase, asymmetrical dimethylarginine (ADMA). We have shown that patients with elevated ADMA levels demonstrated an approximately 75-percent improvement in vascular compliance with sustained-release L-arginine supplementation.³ By contrast, several studies using unselected patients have failed to show benefit from L-arginine administration. Additionally, due to the lack of elevated L-arginine plasma levels or clinical efficacy of L-arginine in this study, one cannot reasonably argue that L-arginine supplementation contributed to the deaths observed. No previous oral L-arginine dietary supplementation study has demonstrated an increased risk of death.

Thus, future studies should be designed with care to select responders to this treatment. The deaths observed in the Johns Hopkins study¹ will make this harder in the future, but as chance was not excluded, this finding should not preclude future research in this area.

Rainer H. Böger, MD
Professor and Head, Clinical Pharmacology Unit
Institute of Experimental and Clinical Pharmacology and Toxicology
Center of Experimental Medicine
University Hospital Hamburg-Eppendorf
Martinistr. 52
D-20246 Hamburg
Germany
E-mail boeger@uke.uni-hamburg.de

1. Schulman SP, Becker LC, Kass DA, et al. L-arginine therapy in acute myocardial infarction. *JAMA* 2006;295:58-64.
2. Bode-Böger SM, Böger RH, Galland A, et al. Pharmacokinetic-pharmacodynamic relationship of the effects of intravenous and oral L-arginine on nitric oxide formation and peripheral haemodynamics in healthy human subjects. *Br J Clin Pharmacol* 1998;46:489-497.
3. Böger GI, Maas R, Schwedhelm E, et al. Improvement of endothelium-dependent vasodilation by simvastatin is potentiated by combination with L-arginine sustained release in patients with elevated ADMA levels [Abstract]. *J Am Coll Cardiol* 2004;34:525A.
4. Doshi SN, McDowell IFW, Goodfellow J, et al. Investigation of the relationship between S-adenosylmethionine, S-adenosylhomocysteine, asymmetric dimethylarginine and endothelial function in healthy human subjects. *Metabolism* 2005;54:351-360.
5. Blum A, Hathaway L, Mincemoyer R, et al. Oral L-arginine in patients with coronary artery disease on medical management. *Circulation* 2000;101:2160-2164.