**Cardiovascular Effects of Asymmetric Dimethylarginine**

*To the Editor:* Kielstein et al.\(^1\) describe the effects of the endogenous nitric oxide synthase inhibitor, asymmetric dimethylarginine (ADMA), in humans in vivo but do not make reference to two previous human studies.\(^2,^3\)

In the original paper describing the presence of ADMA in human plasma and its accumulation in chronic renal failure, Vallance et al.\(^2\) also described the effects of ADMA in isolated blood vessels, on blood pressure in the guinea pig, and on forearm blood flow in healthy human subjects. They described an 8.3% fall in forearm blood flow after an 8 \(\mu\)mol/min ADMA infusion.\(^2\) It was this finding that led the authors to first suggest in 1992 that changes in ADMA could account for cardiovascular abnormalities in humans.

We have recently published a randomized, double-blind, placebo-controlled study in healthy volunteers, looking at the cardiovascular effects of ADMA in humans in vivo.\(^3\) We showed that an intravenous injection of ADMA (3 mg/kg up to a maximum of 250 mg) significantly reduced heart rate and cardiac output (by 9.2% and 14.8%, respectively) and increased blood pressure and systemic vascular resistance (by 6.0% and 23.7%, respectively). Subjects receiving ADMA also showed an impaired cardiac output response to upper limb exercise. Thirdly, our data suggested that ADMA may be extensively metabolized by dimethylarginine dimethylaminohydrolase (DDAH) in humans in vivo.

The experiments by Kielstein et al.\(^1\) now confirm our own published findings and support the conclusions described therein, namely, (1) that increased plasma ADMA concentrations measured in cardiovascular diseases can be associated with prolonged and major cardiovascular effects in humans and (2) that the metabolism of ADMA by DDAH may be an important regulatory mechanism in the human cardiovascular system.

**Vinod Achan, MA, MRCP**

Department of Cardiology
St George’s Hospital Medical School
London, United Kingdom
Vinod.Achan@stgeorges.nhs.uk


**Response**

We appreciate Dr Achan’s interest in our article on the cardiovascular effects of systemic nitric oxide synthase (NOS) inhibition with asymmetric dimethylarginine (ADMA) in humans, originally submitted in October 2002.\(^1\) The seminal study by Vallance et al.,\(^2\) as quoted in the introduction of our paper, sparked the interest on the endogenous NOS inhibitor ADMA. Part of this pioneering work was indeed a small, uncontrolled study on the effect of local intra-arterial ADMA infusion on the forearm arteriolar bed of healthy volunteers.\(^2\) Our study was designed neither to examine the local effect of intra-arterial ADMA infusion nor to look at the effect of a systemic ADMA infusion on a single organ. This should clarify our statement that “controlled trials examining the effects of ADMA on different vascular beds in humans have not yet been reported” (p 172).\(^1\)

Our results, obtained in a series of controlled clinical experiments with state-of-the-art (invasive) assessment of cardiovascular parameters, document for the first time that systemic ADMA administration yielding plasma concentrations in a documented pathophysiologically relevant range, has definite effects on cardiovascular and renal function in humans. It is, therefore, conceivable that ADMA is not only a significant prognostic marker for cardiovascular morbidity and mortality in different patient populations,\(^3,^4\) but above all may cause sustained changes in vascular function and blood pressure.\(^5\) Accordingly, we agree with Dr Achan that a growing body of evidence highlights the pathophysiological importance of ADMA for cardiovascular disease in men.

Jan T. Kielstein, MD
Burecu Improim, MD
Solveig Simmel, MD
Marius M. Hoepner, MD
Hermann Haller, MD
Danilo Fliser, MD

Department of Internal Medicine
Medical School Hannover
Hannover, Germany

Dimitrios Tsikas, PhD
Jürgen C. Frölich, MD

Institute of Clinical Pharmacology
Medical School Hannover
Hannover, Germany

Stefanie M. Bode-Böger, MD, MPH

Institute of Clinical Pharmacology
Otto-von-Guericke-University Magdeburg
Magdeburg, Germany

Cardiovascular Effects of Asymmetric Dimethylarginine
Vinod Achan

Circulation. 2004;109:e327
doi: 10.1161/01.CIR.0000132733.11967.EB

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/109/25/e327

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/