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 μmol/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.

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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 paper 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 that 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.

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