Is Asymmetric Dimethylarginine a Novel Marker of Atherosclerosis?

To the Editor:

In their article, Miyazaki et al\(^1\) demonstrate a correlation between the plasma concentration of asymmetric dimethylarginine (ADMA) and carotid artery intima-media thickness in humans. In multivariate regression analyses, ADMA was the only significant predictor of carotid intima-media thickness besides age and impaired glucose tolerance. However, one critical factor must be carefully evaluated in the interpretation of these data: dimethylarginines are a pair of endogenous, dimethylated L-arginine analogues. ADMA inhibits nitric oxide (NO) synthase,\(^2\) whereas its stereoisomer, symmetric dimethylarginine (SDMA), is biologically inactive.\(^2\) Unfortunately, Miyazaki et al\(^1\) gave only a brief description of the high performance liquid chromatographic (HPLC) method they used to quantify ADMA levels.

When examining the article to which they refer for a description of their method,\(^3\) it seemed that the investigators could not distinguish between ADMA and SDMA with the HPLC system. This is unfortunate because SDMA probably plays no role in vascular lesion formation and, thus, it may have unnecessarily blurred the results of Miyazaki et al.\(^1\) An even greater correlation coefficient between ADMA and carotid artery intima-media thickening might have been found using an analytical method that could unequivocally differentiate between both stereoisomers. Alternatively, there could have been no correlation at all.

Several HPLC methods have been published for the quantitation of methylarginines since the discovery of their biological importance. A major portion of these methods have been unable to differentiate between ADMA and SDMA. Using a recently developed, specific HPLC method that allowed us to clearly separate ADMA and SDMA, we showed that an elevated ADMA concentration is associated with reduced nitrate and cyclic GMP excretion (2 markers for endogenous NO elaboration in vivo) in atherosclerotic humans.\(^4\) Moreover, an elevated ADMA concentration is a risk factor for endothelial dysfunction in hypercholesterolemic humans.\(^5\) Because in animal models of hypercholesterolemia, the pharmacological inhibition of NO synthase accelerates atherosclerosis but the enhancement of vascular NO activity slows the progression of the disease, a defect in the L-arginine/NO pathway may indeed play a decisive role in the initiation and progression of atherosclerosis. In this respect, the study by Miyazaki et al\(^1\) may bring our understanding of the underlying pathophysiology of vascular disease an important step further. Studies like those of Miyazaki et al\(^1\) must be performed using more specific analytical methods to confirm (or reject) their potentially important results. Only then will we know whether ADMA is a novel marker of atherosclerosis.

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Response

We appreciate the comments of Böger and Bode-Böger. They raise an important issue regarding the assay for asymmetric dimethylarginine (ADMA), an endogenous nitric oxide (NO) synthase inhibitor. As they mention, it is critical to distinguish between ADMA and its stereoisomer, symmetric dimethylarginine (SDMA), because SDMA accounts for approximately 25% to 33% of dimethylarginines and it has no effect on NO synthase activity. Therefore, to investigate the pathophysiological role of ADMA in cardiovascular diseases, it is clear that differentiation between ADMA and SDMA is indispensable. We apologize for the brief description of the ADMA assay in our previous works.\(^1-3\) We did separate ADMA from SDMA.

We used the following analytical method for separation. We measured ADMA in the plasma samples using a high-performance liquid chromatography (HPLC) method developed by us.\(^5\) We used the following analytical method for separation. We measured ADMA in the plasma samples using a high-performance liquid chromatography (HPLC) method developed by us.\(^5\) We used the following analytical method for separation. We measured ADMA in the plasma samples using a high-performance liquid chromatography (HPLC) method developed by us.\(^5\) We used the following analytical method for separation. We measured ADMA in the plasma samples using a high-performance liquid chromatography (HPLC) method developed by us.\(^5\) We used the following analytical method for separation. We measured ADMA in the plasma samples using a high-performance liquid chromatography (HPLC) method developed by us.\(^5\)


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