Asymmetric Dimethylarginine and Circulatory Disorders in Postmenopausal Women

To the Editor:

We read with great interest the recent article by Dr Stühlinger et al1 dealing with the relationship among asymmetric dimethylarginine (ADMA), homocyst(e)ine, and endothelial function in young healthy adults, patients with peripheral arterial disease, and older healthy adults. The results of their study demonstrated that experimentally induced hyperhomocyst(e)inemia increased plasma ADMA, an effect that was temporally related to a decline in endothelial vasodilator function. Dr Stühlinger et al1 proposed that ADMA might have a causal role in endothelial dysfunction because there was a significant inverse correlation between plasma ADMA and flow-mediated dilatation of the brachial artery.

Several studies have already reported that endothelial function was strongly influenced by estrogen status and was restored by estrogen replacement therapy in postmenopausal women.2 In a separate series of the study, Dr Stühlinger and colleagues3 showed that inhibition of nitric oxide (NO) bioavailability by ADMA and a subsequent reduction in endothelial dysfunction might contribute to the increase in blood pressure during salt intake in normotensive postmenopausal women not receiving estrogen. It was also demonstrated that estrogen replacement therapy significantly reduced plasma concentration of ADMA in postmenopausal women.4 In a study we presented earlier, it was shown that estrogen-induced improvement of membrane fluidity (the reciprocal value of microviscosity) of erythrocytes was counteracted by ADMA, suggesting that NO might actively participate in the regulation of rheologic behavior of cell membranes and microcirculation in postmenopausal women.5 In this context, it can be speculated that, in postmenopausal women with higher ADMA levels, the circulatory disorders are more pronounced.

The precise mechanisms responsible for the increased ADMA in cardiovascular events in women are still unclear. It is possible that estrogen deficiency after menopause might accelerate abnormalities in endothelial function by increasing ADMA levels. Although only 3 female patients were enrolled in the present study of Dr Stühlinger et al,6 it would be important to explore the gender difference of ADMA kinetics and further to assess more precisely whether the higher ADMA may be associated with increased cardiovascular diseases in elderly women.

Kazushi Tsuda, MD
Ichiro Nishio, MD
Division of Cardiology
Department of Medicine
Wakayama Medical University
Wakayama, Japan
tsudak@mail.wakayama-med.ac.jp


Response

We thank Drs Tsuda and Nishio for their interesting observations related to asymmetric dimethylarginine (ADMA) and estrogen. Estrogen therapy for postmenopausal women is known to improve endothelial vasodilator function.1 The beneficial effect of estrogen on the endothelium has been attributed to its antioxidant properties and to its effect on transcription of NO synthase. Of course, we are intrigued by the observation that estrogen also reduces plasma levels of the endogenous NO synthase inhibitor ADMA,2 which is consistent with the finding that estrogen increases the degradation of ADMA by dimethylarginine dimethylaminohydrolase (DDAH).3 Estrogen joins several other drugs that recently have been shown to improve endothelial function and to reduce plasma ADMA levels, including thiazolidinediones, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and metformin.

We speculate that the effect of these agents to reduce ADMA is related to a property shared by each agent, ie, the capacity to ameliorate endothelial oxidative stress. Elevated levels of angiotensin II and glucose are known to increase vascular generation of oxygen-derived free radicals. Pharmacological antagonism of angiotensin II blocks its effect to increase the activity and expression in the vessel wall of the oxidative enzyme NADPH oxidase. Agents that enhance insulin sensitivity may also ameliorate oxidative stress. By doing so, these agents preserve the ability of DDAH to metabolize ADMA. Under conditions of oxidative stress, DDAH activity is impaired, and ADMA accumulates.4 Our data, and those of others, indicate that this is an important mechanism for the endothelial vasodilator dysfunction that occurs in hyperhomocysteinemia5 and in other metabolic perturbations.

Our study was not designed to examine the effect of gender on the response to methionine challenge. That being said, a reanalysis of the data revealed the possibility of an intriguing dissimilarity between men and women. Although there were no gender differences in plasma homocysteine or ADMA before or after oral methionine, and no gender difference in baseline flow-mediated vasodilation, flow-mediated vasodilation was reduced to a greater degree in male participants 4 hours after the methionine loading test compared with the postmenopausal female patients (2.0±1.3% versus 4.1±1.4%; P=0.034). The postmenopausal women were not using estrogen supplementation.

Accordingly, we agree with Drs Tsuda and Nishio that it would be of interest to conduct additional studies to delineate the interaction of gender differences or hormonal status on homocysteine-induced, ADMA-mediated endothelial vasodilator dysfunction.

John P. Cooke, MD, PhD
Markus Stühlinger, MD
University Clinic of Innsbruck
Innsbruck, Austria
Falk Cardiovascular Research Center
Stanford University School of Medicine
Stanford, Calif


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Kazushi Tsuda and Ichiro Nishio

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