Letter by Tsuda Regarding Article “Endothelial Activation in Lacunar Stroke Subtypes”

To the Editor:

We read with great interest the recent article by Knottnerus et al1 dealing with the relationship between endothelial activation and lacunar stroke subtypes. The results of their study demonstrated that tissue plasmonogen activator activity, a circulating blood marker of endothelial function, was increased in patients with white matter lesions (WML); WML is a subtype of lacunar stroke caused by a diffuse small vessel disease. In addition, it was demonstrated that plasmonogen activator inhibitor type 1 antigen levels were lowest in patients with WML. The authors propose that differences in the activity of components of the fibrinolytic system might contribute to WML development in lacunar stroke.

Numerous studies have focused on the vascular protective effects attributable to nitric oxide (NO) and have shown that hypertension, as well as vascular dysfunction, may be associated with impaired NO metabolism. Khan et al2 examined the relationship between the endogenous NO synthase inhibitor, asymmetric dimethylarginine (ADMA), and cerebral small vessel disease; they showed that plasma ADMA levels were elevated in small vessel disease and were significantly correlated with leukoaraiosis severity, suggesting that ADMA might be associated with small vessel disease and mediate small perforator damage. It was also demonstrated that intravenous infusion of ADMA decreased heart rate and cardiac output, as well as increased mean blood pressure in humans.3 Conversely, Scuteri et al4 demonstrated that inhibition of NO bioavailability by ADMA and a subsequent reduction in endothelial function might contribute to the increase in blood pressure during salt intake in normotensive postmenopausal women not receiving estrogen. In a study presented earlier, we showed that plasma ADMA levels were increased in hypertensive subjects compared with normotensive subjects,5 indicating that the higher plasma ADMA levels might be accompanied by hypertension and vascular dysfunction. In addition, we demonstrated that membrane fluidity of erythrocytes (a reciprocal value of membrane microviscosity) in hypertensive subjects was associated with decreased NO metabolite and increased ADMA levels in plasma.6 The findings suggest that NO and ADMA might have a crucial role in the regulation of rheological behavior of cell membranes. The reduction in membrane fluidity of erythrocytes by ADMA could cause a disturbance in microcirculation, which could contribute to the pathophysiology of circulatory disorders in the brain.

In this context, it can be speculated that, in patients with WML, endothelial dysfunction might be more pronounced. Although the authors demonstrated that there was no difference in hypertension prevalence between WML and isolated lacunar infarct, we would like to know whether the magnitude of blood pressure and the indices of endothelial dysfunction, such as plasma ADMA levels, might be associated with the tissue plasmonogen activator activity, levels of plasmonogen activator inhibitor type 1, or severity of WML in the study of Dr Knottnerus et al. It would be important to assess more precisely the mechanisms underlying WML and their contribution to the progression of lacunar stroke.

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