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Colin P. Derdeyn

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Miyazawa et al (page 243) in this issue of the *AJNR* compare the natural history of asymptomatic patients with middle cerebral artery (MCA) occlusion to those with internal carotid artery (ICA) occlusion. In addition, they report an association between the appearance of new ischemic lesions on MR images and the presence of hemodynamic impairment.

Clinical studies investigating hemodynamic risk factors for stroke, such as the present one, are complicated for many reasons. Many physiological, clinical, and epidemiologic issues remain largely undefined. Current clinical methods of hemodynamic assessment rely on different hemodynamic mechanisms and are indirectly made on the basis of assumptions (some likely inaccurate) regarding underlying physiological processes. The pathophysiological mechanisms by which severe hemodynamic impairment might predispose to ischemic stroke are not known. Furthermore, the association between an abnormal result with most, but not all, of these clinical methods and stroke risk is unproven (1). Empirical proof linking an abnormal hemodynamic response and the risk of future stroke is required for each of the available techniques of hemodynamic assessment. Much important data remain to be gathered in this area and must be done in a rigorous manner. Finally, once an association has been established, the next job is to prove that the relationship is causal: ie, fixing the hemodynamic abnormality, through medical or mechanical intervention, fixes the stroke risk. The pilot data of Miyazawa et al published in this issue of the *AJNR* should be interpreted with these thoughts in mind.

When an artery becomes severely narrowed or completely occluded, the pressure in the vessel beyond the lesion can fall. The arterial pressure in the distal circulation supplied by that vessel will depend not only on the degree of narrowing, but also on the capacity of collateral vessels to provide blood flow. The circle of Willis provides adequate collateral flow for many patients with complete occlusion of the common or ICA, for example (2). In some patients, however, these collateral channels do not maintain normal arterial pressure. Experimental studies, generally in animals and involving acute and severe hypotension, have shown that the initial reflex response of the cerebrovasculature is autoregulatory vasodilation of small arterioles (3). This serves to maintain normal blood flow by reducing vascular resistance. With further reductions in pressure, autoregulatory capacity is exceeded and blood flow falls passively as a function of pressure. Ischemic symptoms do not necessarily develop with this fall in blood flow, as the brain can increase the fraction of oxygen extracted from the blood (oxygen extraction fraction) and maintain normal oxygen metabolism and brain function (4). The degree to which these different physiological responses to reduced perfusion pressure remain present in humans with chronic disease is not known, however.

In addition, the mechanism by which severe hemodynamic impairment might lead to subsequent ischemic infarction is not established. One hypothesis is that the presence of severe hemodynamic impairment may increase the chance of ischemic injury due to an embolic event. Transcranial Doppler studies have reported frequent clinically silent embolic events in patients with atherosclerotic disease (5). An embolus lodging in a vessel in which the arterial pressure and blood flow are low and the oxygen extraction of the tissue is already maximal may be more likely to cause ischemic injury. This hypothesis is supported by animal studies employing a microsphere model of embolic stroke in normal and collateralized hemispheres (6).

The determination of hemodynamic impairment in living humans is generally made by inference, by use of one of three different clinical approaches. The first two theoretically test for the presence of autoregulatory vasodilation. In the first method, the presence of autoregulatory vasodilation is inferred when a normally robust CBF or blood velocity response to a vasodilatory challenge is dampened or absent. A paired-flow technique was used in the study of Miyazawa et al, with quantitative measurements of CBF made with stable xenon CT (Xe-CT) before and after the administration of acetazolamide, a potent vasodilator. In the second approach, the presence of autoregulatory vasodilation is presumed when measurements of mean transit time or cerebral blood volume are increased. The third approach relies on measurements of increased oxygen extraction.

The correlation between these methods can be quite poor (1). For example, hemodynamic studies of patients with carotid occlusive disease comparing the vasodilatory effects of acetazolamide to hypercapnia or physiological activation have reported striking discordances (7, 8). Kazumata and colleagues measured an increase in CBF associated with hypercapnia in 10 of 11 patients who manifested an absent increase or paradoxical reduction in CBF after acetazolamide administration (8). The vasodilation in response to acetazolamide is mediated by different mechanisms than that due to autoregulation (9). An additional confounding factor with the use of Xe-CT for the measurement of CBF is that xenon itself is also a potent vasodilator. Rather than the analogy of the blind men feeling different parts of the elephant and reaching differ-

ent conclusions on the nature of an elephant, in this situation, the blind men may be feeling different elephants.

Empirical proof of an association between an abnormal result obtained from each of these tests and the risk of subsequent stroke is required. Baseline stroke risk factors, such as hypertension, smoking, and hyperlipidemia must be assessed. Differences in stroke risk observed between groups might be due to differences in these factors rather than hemodynamic abnormalities. Therefore, clinical studies designed to prove such an association must incorporate several of the following factors.

First, the patient population must be well defined and unambiguous, in terms of presence of prior ischemic symptoms and the type of arterial lesions. The data from the current study and others illustrate the need for this requirement. The risk of stroke in patients with asymptomatic carotid occlusion is very low and likely related to the low incidence of hemodynamic impairment in this population (10). Conversely, the incidence of hemodynamic impairment is likely quite high in patients with MCA occlusion (11). Second, the hemodynamic risk factor must be prospectively defined (not a retrospective determination of the threshold for an abnormal test predicated on the knowledge of patients' outcome). Third, the comparison of the high- and low-risk groups (determined by the hemodynamic test) and the outcome (stroke or new ischemic lesion determined by MR imaging) must be statistically sound (survival curve analysis rather than chi-square tests, for example). Finally, the independence (multivariate analysis against other stroke risk factors) and the strength of the association must be assessed. To date, the strongest evidence supporting a test of hemodynamic assessment as a predictor of stroke risk is for the measurement of increased oxygen extraction fraction with positron emission tomography in patients with carotid artery occlusion (1, 12).

In the study of Miyazawa and colleagues in this issue of *AJNR*, asymptomatic patients with MCA occlusion (n = 18) or ICA occlusion (n = 17) were identified with MR angiography during MR examinations of 3965 patients with nonischemic neurologic symptoms. Paired measurements of CBF, before and after the administration of actazolamide, were made with Xe-CT. The timing of Xe-CT relative to study enrollment was not specified, nor was the definition of an abnormal blood flow response (the threshold level defining normal from abnormal). Baseline clinical and epidemiologic risk factors for stroke were not categorically recorded or analyzed. All patients underwent follow-up MR imaging (an average of 3.8 times at unspecified intervals). The method of clinical follow-up was not described.

Although not statistically significant, clinical ischemic events occurring during the follow-up period were more common in patients with MCA occlusion (four of 18, compared with one of 17 patients with carotid occlusion). Three of these five ischemic events were in the territory of the initial arterial lesion. Asymptomatic infarction was found in seven patients (five with MCA occlusion and two with ICA occlusion). The location of the asymptomatic lesions relative the arterial occlusion was not reported. As a group, patients with new lesions (both asymptomatic and symptomatic) had significantly lower CBF responses to acetazolamide than did patients with no new lesions manifested by MR imaging. The relationship between hemodynamic impairment and the appearance of new lesions in individual patients was not explored.

The study of Miyazawa and colleagues provides important pilot data on the prognosis of asymptomatic MCA occlusion. These patients had a high risk for the development of clinical stroke or silent infarction (50%). It is possible that this risk may have been because of a high incidence of hemodynamic impairment. A well-designed, prospective study of hemodynamic factors and stroke risk in this patient population is warranted.

COLIN P. DERDEYN, M.D.
Member, Editorial Board

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