EDITORIAL COMMENT

Protecting the Brain: How Do We Measure Success?*

Jay S. Yadav, MD, FACC, FSCAI
Cleveland, Ohio

The rationale for carotid revascularization, surgical or interventional, is to reduce the patient’s future risk of stroke. Unfortunately, carotid revascularization itself poses a risk of stroke, and enormous efforts have been made in refining both surgical and interventional techniques to reduce peri-procedural stroke risk. The incidence of stroke during carotid endarterectomy (CEA) has been reduced by use of perioperative aspirin and intraoperative heparin, electroencephalogram, and transcranial Doppler (TCD) monitoring and shunting when necessary to prevent hemispheric ischemia. For carotid stenting, the Achilles heel has always been embolization, and indeed, many felt that carotid stenoses could never be treated with angioplasty, because of the brain’s intolerance of embolization. This concern explains why even though carotid angioplasty was proposed in 1977 and first performed in 1980, it has been only in the last few years that carotid angioplasty and stenting (CAS) has been considered a viable alternative to CEA (1–3).

See page 1007

Historically, stroke is a clinical diagnosis based upon the history and neurological examination. All of the major randomized trials of CEA, such as the North American Symptomatic Carotid Endarterectomy Trial and the Asymptomatic Carotid Atherosclerosis Study (ACAS), used the clinical diagnosis of stroke as the primary end point (4,5). Unlike myocardial infarction, adequate serum biochemical markers have not been developed for central nervous system necrosis or injury. This lack of an easily measured surrogate has been problematic for stroke neurologists for years and now has become a problem for interventional cardiologists as carotid stenting enters the mainstream. The peri-procedural stroke rate for carotid stenting with emboli protection is sufficiently low that a clinically relevant surrogate that occurred at a greater frequency would be required for both research and clinical purposes. In this issue of the Journal, Schlüter et al. (6) take an important step in this direction with their prospective use of diffusion weighted (DW) magnetic resonance imaging (MRI) in patients undergoing carotid stenting with emboli protection. In 42 patients, there was one stroke, but post-interventional DW MRI lesions were observed in 10 patients (23%).

Diffusion weighted MRI measures the apparent diffusion coefficient (ADC) of water. Reduction in the ADC happens within minutes of the onset of ischemia in animal models of stroke and is thought to be due to a failure of high-energy metabolism, loss of ion homeostasis, and cytotoxic edema (7,8). Initially, it was felt that DW MRI lesions represented irreversible brain injury and were a surrogate for clinical stroke. More recent animal and human studies indicate a heterogeneity of DW MRI findings in acute stroke, with many patients having complete resolution of the ADC abnormalities within a few days (9,10). It is reasonably clear now that, according to Fiehler et al. (10), “ADC decreases do not reliably indicate tissue infarction.” In keeping with this, Schlüter et al. (6) found that except for the patient with a clinical stroke, follow-up MRI scans were normal in all patients with DW MRI lesions who had normal neurologic exams.

Others have also tried to use MRI to detect subclinical embolization and brain infarction after carotid revascularization. In a Danish study of 33 CEA patients, eight (24%) had new MRI lesions, but only three (8%) had either transient ischemic attacks (TIAs) or strokes (11). In a German study of 51 CEA patients, 12% had new DW MRI lesions post-operatively, whereas only 4% had new neurologic deficits (12). In another German study of 77 CEA patients, 34% had new DW MRI lesions, yet only 6% had TIAs or strokes (13). None of these studies included a follow-up MRI to assess the permanence of the post-procedural MRI lesions. Prospective studies using MRI scanning after CAS show a similar frequency of MRI lesions and lack of correlation with clinical findings. In a study of 72 patients undergoing CAS with emboli protection, there were three (4.2%) strokes and two (2.8%) TIAs, but 11 (15%) had new DW MRI lesions (14). Interestingly, these investigators also performed TCD to detect emboli during the procedure and did not find a correlation between emboli load by TCD and DW MRI lesions (14,15).

Transcranial Doppler has been used extensively to study embolization in patients with carotid and cardiac disease and a variety of procedures ranging from cardiac catheterization to coronary artery bypass grafting. Unfortunately, it remains limited by the inability to reliably differentiate gaseous from particulate emboli or quantify particle size (16). Transcranial Doppler was used in our very first carotid angioplasty patients to help us understand which parts of the procedure caused embolization (Fig. 1). Several studies have demonstrated a reduction in the number of high-intensity transients by approximately 70% to 80% when emboli prevention devices are used (17,18). It should be noted that TCD is a very sensitive tool, and frequent high-intensity transients are noted in patients undergoing cardiac catheterization and in asymptomatic patients with carotid stenosis while resting in bed (19–21). Indeed,
bedside TCD monitoring has revealed that spontaneous microembolization to the brain is fairly common and surprisingly well tolerated. Animal studies with embolization of various size carotid plaque fragments have demonstrated that particles <200 μm in diameter are well tolerated without ischemic changes (22). These findings help to explain why even unprotected carotid stenting had surprisingly good clinical results.

Ideally, there would be serum biomarkers for stroke analogous to creatine protein kinase MB fraction and troponin for myocardial infarction. Unfortunately, the blood brain barrier limits the release of markers of central nervous system injury into the bloodstream. S-100B, neuronal enolase, thrombomodulin, and myelin basic protein have all been evaluated for this purpose, with most of the effort directed at S-100B and neuronal enolase. For acute stroke, small pilot studies have shown a positive correlation between infarct size, clinical outcome, and serum levels of S-100B and neuronal enolase (23–25). For carotid endarterectomy, however, there has been a lack of correlation between clinical events and serum levels of these proteins (26,27).

There was only one stroke in the Schlüter et al. (6) study, but it was in the contralateral hemisphere, not in the distribution of the treated artery. The occurrence of an event in the untreated carotid or vertebral artery is not infrequent, and with the advent of emboli prevention devices reducing the number of ipsilateral ischemic complications, up to 25% of all strokes associated with carotid stenting may be in the contralateral hemisphere (28). Clearly, adequate operator experience and better sheath and guide catheters for carotid access will be mandatory for the widespread successful application of carotid stenting. Carotid access remains the most challenging part of the carotid stenting procedure, yet industry has devoted minimal resources to developing specialized access devices for the carotid.

We have made remarkable progress in developing percutaneous treatments for stroke prevention that equal or exceed surgical repair, but further improvement is possible and needed. A surrogate for clinical stroke would certainly facilitate the development and evaluation of new technology and methods for carotid stenting. A biomarker that is analogous to creatine protein kinase for coronary intervention would be the most practical and cost effective. Although there are a number of tests at our disposal that are potentially more sensitive than the neurologic examination for assessing brain injury, none of them has yet been shown to be an accurate surrogate for the clinical diagnosis of stroke, and certainly DW MRI lesions cannot be considered to always represent brain infarction. For the time being, the gold standard for measuring ischemic brain injury, either spontaneous or post-procedural, remains a careful neurologic examination.

Reprint requests and correspondence: Dr. Jay S. Yadav, Director, Vascular Intervention, Department of Cardiovascular Medicine/F25, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: yadavj@ccf.org.

REFERENCES
5. European Carotid Surgery Trialists’ Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. Lancet 1991;337:1235–43.


