Cerebral Hemodynamics in Carotid Occlusive Disease

The article by Wilkinson et al, in this issue of the *AJNR* raises several important physiological and clinical issues regarding patients with atherosclerotic cerebrovascular disease: 1) the high frequency of hemodynamic impairment among patients with symptomatic stenosis, which is an observation that points to the synergy of hemodynamic and embolic mechanisms in the pathogenesis of stroke in these patients; 2) the time course for recovery of normal hemodynamics in humans with chronic regional reductions in perfusion pressure; and 3) the variability of different perfusion measurements, particularly the relative insensitivity of cerebral blood volume (CBV) measurements for autoregulatory vasodilation.

Hemodynamic impairment is a term generally used to describe the presence of reduced cerebral perfusion pressure. Cerebral perfusion pressure for any brain region equals the mean regional arterial pressure minus the venous pressure or intracranial pressure, whichever is higher. In patients with occlusive arterial disease, perfusion pressure is generally equated to mean arterial pressure. Whether stenosis or occlusion will cause reduction in the mean arterial pressure of cortical arteries depends on the presence and degree of stenosis but more importantly on the status of the collateral circulation. The large majority of patients with asymptomatic carotid occlusion have no evidence of hemodynamic impairment, for example (1). Circle of Willis and/or external to internal collaterals are sufficient to maintain normal perfusion pressure in these patients. This observation indicates the fallacy of the term *hemodynamically significant stenosis* when applied to arterial stenosis >70% in the cerebral circulation.

We do not routinely measure mean arterial pressure or perfusion pressure in brain arteries to identify the presence of hemodynamic impairment. Instead, we rely on physiological imaging studies to identify or infer the presence of normal compensatory mechanisms to reduced perfusion pressure (2). When the mean arterial pressure in a cortical artery decreases, two compensatory responses may occur (3). By means of these two responses, normal oxygen metabolism and brain function are preserved. The first is autoregulatory vasodilation of the small distal arterioles. This serves to reduce vascular resistance and maintain cerebral blood flow (and the delivery of oxygen and glucose) at near normal rates (4). The second response occurs when blood flow decreases. To maintain normal oxygen metabolism and normal neurologic function, neurons may increase the fraction of oxygen extracted from the blood (oxygen extraction fraction) (5). The average baseline oxygen extraction fraction is approximately 30% and can increase to 80%. These two mechanisms may occur simultaneously (3): cerebral blood flow decreases slightly through the autoregulatory range, leading to slight but measurable increases in oxygen extraction fraction (6). When autoregulatory capacity is finally exceeded, blood flow decreases more rapidly and oxygen extraction fraction increases dramatically (7).

Different physiological imaging tests assess different compensatory mechanisms (2). Paired flow studies compare a baseline measurement of blood flow or blood velocity with a second measurement after a vasodilatory stimulus. The existence of preexisting autoregulatory vasodilation is inferred if blood flow or blood velocity does not increase normally. A second category of studies is also intended to identify autoregulatory vasodilation. These studies involve measurements of mean transit time directly or by calculation from the ratio of independent measurements of cerebral blood flow and CBV. The method used in the current study falls into this category. Mean transit time is equal to the ratio of CBV over blood flow by the central volume theorem. Mean transit time increases with autoregulatory vasodilation (8). CBV also increases, but this response may be variable for a number of reasons, as described below. The final category of studies uses direct measurements of oxygen extraction fraction.

In the present article by Wilkinson et al, baseline measurements of first moment transit time, a first pass area under the curve analysis of an intravascular tracer, were significantly prolonged in the affected middle cerebral artery territory. These data are consistent with previous reports regarding patients with symptomatic carotid stenosis or occlusion. As a group, these patients consistently have significantly greater degrees of hemodynamic impairment when compared with normal control participants or asymptomatic patients with similar degrees of stenosis (9, 10).

Not all patients with symptomatic stenosis or occlusion have evidence of hemodynamic impairment; however, those who do have a much higher risk of subsequent stroke disease (11–14). What is the mechanism of stroke in these patients? The data presented above and others discussed below suggest a powerful synergy between hemodynamic and embolic mechanisms. Clinically silent emboli are commonly identified in vessels distal to symptomatic carotid stenosis (15). Animal studies have shown that for a given embolic event, the size of infarction is markedly increased if preexisting hemodynamic impairment is present (16). Furthermore, based on animal studies, some evidence exists that increased baseline levels of cerebral blood flow are protective against ischemic injury (17). In humans, we have proof that the presence of hemodynamic impairment, identified by some but not all imaging methods, is a powerful and independent risk factor for stroke in patients with carotid atherosclerotic occlusive disease (11–14). It is likely

that nearly all strokes in these patients occur because of embolic material and that the presence of hemodynamic impairment increases the chances that an embolic event will result in an ischemic stroke.

The relative importance of hemodynamic and embolic mechanisms is a moot point for symptomatic patients with severe carotid stenosis, because the benefit with revascularization is so dramatic, regardless of the mechanism (18). Determination of hemodynamic status may have great potential for two other patient populations, however: patients with complete carotid occlusion and those with asymptomatic carotid stenosis. Hemodynamic impairment, as identified by some but not all physiological imaging methods, has been proved to be a powerful and independent risk factor for stroke in patients with symptomatic carotid occlusion. A multicenter, randomized clinical trial of surgical revascularization (external to internal carotid artery bypass) for patients with symptomatic carotid occlusion and increased oxygen extraction fraction is underway (Carotid Occlusion Surgery Study, National Institutes of Health, National Institute of Neurological Disorders and Stroke, NS39526).

The prevalence of hemodynamic impairment in patients with asymptomatic carotid occlusive disease is very low (1, 19). This low prevalence may account in part for the low risk of stroke with medical treatment and, consequently, the marginal benefit with revascularization. The absolute annual risk reduction for carotid endarterectomy reported in the Asymptomatic Carotid Atherosclerosis Study was 1% (20). The presence of hemodynamic impairment may be a powerful predictor of subsequent stroke in this population (19). This is one area of research with enormous clinical implications: if a subgroup of asymptomatic patients who are at high risk because of hemodynamic factors could be identified, it would be possible to target surgical or endovascular treatment at those most likely to benefit.

The second issue raised in this article is the time course of recovery of normal hemodynamics. To my knowledge, this is the first report to study humans within hours of revascularization. A number of animal studies involving short-term responses to reduced and increased cerebral perfusion pressure have been published. The degree to which the data from these studies are relevant to humans with chronic, regional reductions in perfusion pressure is unclear. Studies such as the one presented by Wilkinson et al are important for defining these physiological changes.

Finally, these data illustrate the variability of different perfusion indices for identifying hemodynamic impairment. They are not interchangeable. We infer the presence of reduced perfusion pressure by indirect evidence for the presence of normal compensatory mechanisms. These mechanisms were defined primarily in animal studies of acute global reductions in perfusion pressure. Furthermore, the degree to which results from one physiological imaging test correlate with results from another in a given patient may be extremely variable (2). Tests must be validated against patient outcome; one cannot assume that an abnormal test result indicates an increased risk of stroke.

In the study presented by Wilkinson et al, measurements of relative CBV showed little change between middle cerebral artery and other regions at baseline or between baseline and follow-up studies despite the large changes in first moment transit time. This is consistent with other studies and was discussed in some detail by our group in a recent article in *Brain* (3). First, the relationship between CBV and autoregulatory vasodilation is not linear or direct. The autoregulatory changes occur at the level of small penetrating arterioles. These vessels represent a small fraction of total CBV. The largest component of CBV is venous, and the degree to which autoregulatory vasodilation leads to increased CBV may be variable. Second, there may be physiological variability between patients in the relationship between CBV and autoregulatory vasodilation. Data regarding CBV changes through the autoregulatory range and beyond in animal studies have been variable: some have shown a dramatic increase, others a slight increase, and others no increase (21–23). Human studies indicate that individual variability seems to occur (3). Third, it may be difficult to accurately measure changes in CBV due to autoregulatory vasodilation. Normal CBV is approximately 4%. A 25% increase in CBV would increase this to 5%, which would be a 1% change in an imaging voxel. This may be difficult to accurately identify. Finally, different imaging methods may be more or less sensitive to these small changes. If the largest changes in CBV are seen in pial veins, techniques that are more sensitive to parenchymal vessels would be less sensitive to these changes.

In summary, the article by Wilkinson et al in this issue of *AJNR* is an important contribution to the literature regarding the time course of improvement of hemodynamic impairment. In addition, it also raises two other clinically relevant issues. First, it indicates the importance of hemodynamic mechanisms in the pathogenesis of ischemic stroke. Physiological imaging may come to play an important role in selecting patients with asymptomatic carotid stenosis for revascularization and for patients with complete carotid occlusion. Second, it illustrates the variability of different imaging tools in identifying hemodynamic impairment and the need to correlate these tests with meaningful patient outcomes. All three areas are important directions for future clinical research.

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Perfusion MR and the Evaluation of Meningiomas: Is It Important Surgically?

In their article in this issue of the *AJNR,* Yang et al very nicely present their data analyzing dynamic perfusion curves and permeability between intra- and extravascular compartments, to determine whether this information can be used to differentiate typical from atypical meningiomas. Specifically, permeability quantitatively assessed and expressed as the volume transfer constant is increased, because of capillary leakiness, among other factors, that is more commonly found in atypical meningiomas. Thus, the authors propose that the volume transfer constant, as opposed to cerebral blood volume, can be used to distinguish atypical from typical meningiomas, which presumably should have some value to the surgeon, as well as the neurooncologist, following the resection. Thus, this serves as a potentially useful surrogate marker, unlike anatomical MR images, to alert the surgeon to the fact that the lesion they are about to operate on may behave differently than the typical meningioma. The real question is whether this makes a difference to the surgeon.

One very important component of the presurgical planning is to make some assessment regarding the vascularity of the lesion with regard to its feeding arteries. In the typical convexity meningioma, interventional techniques to embolize these feeders can be exceedingly helpful before surgery. As surgeons, we once believed that this had to be done immediately before the resection, but we now know this is not the case and have found that delayed surgery after embolization, of as much as a week or 10 days, can actually soften the tumor and continue to reduce the blood supply to the point where it affects the need for postoperative transfusion. Thus, the concept of preoperative embolization is an important one and would be made regardless of the finding on perfusion imaging to detect a change in vascular permeability. Embolization is preferred in all meningiomas preoperatively, although we realize the limitations, especially with meningiomas at the skull base that often are not amenable to any significant degree of embolization. Another factor that influences the surgeon in the preoperative phase of assessing a patient with a presumed meningioma is whether in an asymptomatic situation, in which the tumor is small and discovered by serendipity, the lesion needs to be removed. It is becoming more frequent to see patients presenting with small meningiomas having had scans for other reasons. In this setting, the knowledge that the tumor is more likely atypical, based on perfusion imaging,

would influence a nonconservative approach toward resecting the lesion sooner than later. To this end, the information presented in a study such as this would be most useful and beneficial to the patient.

The goal of the operative procedure is to always achieve a complete, or Simpson grade I, resection. In doing this, one strives to remove at least 1 cm of normal dura around the lesion. Often during surgery, the surrounding dura is hyperemic from a proteinaceous coating due to compressed arachnoid and does not represent tumor invasion. Notwithstanding, we always strive to remove at least 1 cm, if not more, of the surrounding margin during the course of the procedure. This would be true for both atypical and typical meningiomas, and in fact we surgeons do not know whether the degree of peripheral dural resection should be greater in atypical meningiomas and whether it would affect outcome in terms of recurrence. Thus, the bone flap—ie, size of the craniotomy—and strategy to remove a margin of dura would not be affected by knowing the quantitative assessment of vascular permeability. One factor that would be influenced by this information, however, would be the strategy of resecting a normal rim of brain in terms of needing to do this, because these atypical meningiomas can have invasive features into the adjacent brain. This might not be very important in nonfunctional regions, but when atypical meningiomas invade brain in functional regions, such as near the Rolandic cortex or in the dominant hemisphere, functional mapping techniques can be very useful in determining the safety of the procedure. Therefore, the information that could be used preoperatively to predict that the tumor is atypical and has brain invasion would be useful in planning whether or not a functional mapping procedure would be indicated. Once the operation proceeds however, the resection is as one would expect—ie, aggressive and radical—regardless of the pathology. The frozen-section information would not change the overall goal of the operation. In most circumstances, when an atypical meningioma is found, the goal is to watch carefully with serial imaging studies spaced closely together in the postoperative period. If the tumor is incompletely resected, this could influence the desire to treat with conformal radiation or radiosurgery sooner rather than later, and it is in this setting that the pathology ultimately dictates the direction of treatment in the postoperative stages. This is not, however, an important factor to preoperatively influence the surgeon.

In essence, the information provided in this article will be quite useful to surgeons in helping to plan the surgical strategy. Although the ultimate goal—ie, complete or radical resection—will not change, this information could help avoid surprises such as brain invasion that could be successfully planned for if this information were available preoperatively.

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