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Commentary

Imaging Cerebral Blood Flow in Interventional Neuroradiology: Choice of Technique and Indications

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In this issue of the *AJNR*, Tarr et al. [1] present serial measurements of cerebral blood flow (CBF) obtained by using xenon CT in eight patients having staged embolization of arteriovenous malformation (AVM). Tarr et al. used administration of acetazolamide and repetition of the blood-flow study to challenge the cerebral vasculature and test for autoregulatory reserve. They obtained a baseline and a single CBF study after embolization in six patients. Two patients had more than one CBF study after embolization. The times of study were from 1 to 26 days after embolization. Twenty percent of the attempted studies (two patients) could not be completed because the patients had anxiety attacks.

Analysis of data consisted of calculation of flow in 169 regions of interest 2 cm in diameter. The mean CBF before embolization was 49.9 ml/100 g/min, and the mean CBF after embolization was 56.8 ml/100 g/min.

The authors categorized augmentation as normal if it was ≥10% and as decreased if it was <10%. This was despite a mean SD of blood-flow measurement within the region of interest of 19.1 ml/100 g/min or 38% of the mean total blood flow. Using their criteria, they found that mean augmentation after embolization was significantly diminished relative to the augmentation before embolization. Seven of eight patients had one or more parenchymal areas that showed diminished augmentation of flow after embolization. The authors also noted significant differences in response to acetazolamide after embolization. These differences were based on six studies obtained between days 1 and 5 after embolization (two of them in the same patient), two studies in one patient obtained between days 6 and 10, and three studies obtained between days 11 and 26.

In their discussion, Tarr et al. address the issue of the timing of multistaged AVM treatment. They point out that some authors have recommended a short interval between embolization and surgery to prevent the reconstitution of the AVM nidus through collateral circulation. They state that they themselves have observed that recruitment rarely occurs quickly after partial embolization of a nidus. Only two patients in a previous study [2] by Tarr et al. had had embolization. This may not have been a sufficient number of cases. My colleagues and I have seen angiographically demonstrated recruitment as soon as 3 weeks after embolization, although it is uncommon. We think, however, that it is an ominous development and that it should be factored into the decision as to when surgery should be performed after embolization.

Following their observation of the rarity of recruitment, Tarr et al. conclude that their results support a time delay between successive stages of embolization or between embolization and surgery to allow the cerebral vasculature to accommodate the hemodynamic changes caused by embolization. They conclude further that the timing of staged procedures should be individualized because of the variability of hemodynamic effects among patients. It would be difficult to argue with the notion that the timing of staged procedures should be individualized. However, their study should be examined more closely with regard to statistical techniques to see if the results support their conclusions adequately to warrant modification of patient care.

This article is a commentary on the preceding article by Tarr et al.

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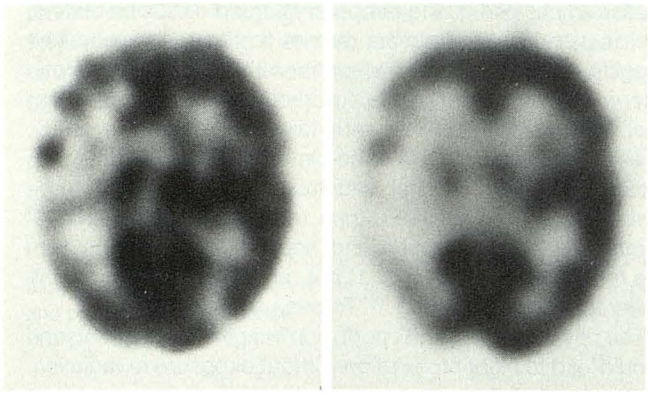

Fig. 1.—Single-photon emission CT (SPECT) scans obtained by using a dual isotope technique in a patient with left-sided hemiparesis. *Left*, Resting image of ^{99m}Tc-HMPAO flow (20 mCi [740 MBq] dose). Five minutes after resting image was acquired, patient was given 1 g of acetazolamide IV and 20 min later was given 4 mCi (148 MBq) of ^{123}I-iodoamphetamine IV. After 15 min, a single volume acquisition was performed by using dual windows for ^{99m}Tc and ^{123}I. *Right*, ^{123}I-iodoamphetamine SPECT scan obtained at this time shows large flow defect in right middle cerebral artery territory, consistent with loss of vasodilatory reserve in a region that was hypoperfused only slightly on baseline study. (Courtesy of Michael D. Devous.)

Assessment of the significance of the study by Tarr et al. must take into account that it involved only eight cases. Furthermore, in only two cases were the studies performed more than once after embolization. The ability to achieve statistical significance in so many areas of analysis depends on the approach taken by the authors of examining multiple regions of interest in each patient's brain. This leads to a multiplication of any effect seen in any one patient. This multiplication factor in this analysis led to an *n* of 169 parenchymal areas rather than an *n* of eight patients. This approach properly considers that differences exist from one part of the brain to another when AVMs are present. However, it tends to magnify any effects that are manifested broadly in any one patient or any inconsistency between patients in the number of regions analyzed.

Acetazolamide, a carbonic anhydrase inhibitor, creates vasodilatation via the same metabolic pathway as the carbon dioxide effect. Thus, in the acetazolamide challenge test, that pathway is an intrinsic part of the experimental variable [3]. Thus, corrections cannot be made for the effects of carbon dioxide as Tarr et al. did in their study.

With these limitations in mind, we must ask what is the lesson of this study. Areas of low flow around AVMs have been shown with xenon CT and other CBF imaging techniques [4–6], as has the increase in CBF after embolization on xenon CT scans [7]. Impaired cerebral vasoreactivity may be an indication of disordered autoregulation after embolization or a reflection of the underlying overall increase in the rate of blood flow, above which augmentation may be more difficult. Tarr et al. are to be congratulated for their application of CBF technology in the interventional setting and for their advocacy of attention to cerebral flow effects.

As we apply CBF determinations in other interventional settings, it is appropriate to ask which technique is best and what the limitations are of one technology relative to another. I think that xenon CT has significant limitations that might be tolerable if it were quantifiably reliable for determinations of blood flow. However, I do not share the confidence of Tarr et al. in the legitimacy of the numerical flow values obtained with xenon CT.

The presence of adjacent gray matter, white matter, and cerebral sulci detracts from the quantifiable aspects of xenon CT. This is evidenced by the large SDs that are seen in calculations of regions of interest. The SD can be minimized by shrinking the size of the region of interest. However, then sampling error sets in. These problems were alluded to by Rottenberg et al. [8].

Another confounding effect in the quantifiable reliability of xenon CT scanning is the pharmacologic effect of a xenon concentration of 30% on CBF. Dettmers et al. [9] showed increased flow and altered autoregulation in baboons administered 35% stable xenon. They also found altered electroencephalographic activity (slowing) and various CBF effects in a group of volunteers administered xenon. Using transcranial Doppler sonography, my colleagues and I [10] found significant effects in normal volunteers who inhaled 30% xenon. Flow velocity increased significantly not only as a function of xenon concentration but also over a time interval coincident with that of scan acquisition. This was particularly disturbing because, insofar as velocity reflects flow, the effects on the calculated blood flow value could have been skewed markedly as the blood flow itself changed during the study. The severity and time course of the effects also varied substantially between subjects. This also complicates interpretation, because the technique of xenon CT depends on repeated observation over time. Other animal studies [11] also have shown pharmacologic effects. Although the effect of xenon may tend to be global rather than tissue specific, the fact that it does not affect each individual equally makes flow values unreliable.

Good and Gur [12] and Stringer [13] recently discussed the accuracy of xenon CT measurements in relation to a computer model for predicting effects on derived flow values based on scanning protocols. This approach assumed a linear effect during inhalation after a 1.5-min delay and noise-free enhancement, neither of which occurs reliably in vivo. Linearity of enhancement is not established, and the enhancement is not noise-free. Enhancement is unpredictable in its occurrence, degree, and timing between subjects. Different subjects show activation at different times to different degrees at different rates during administration.

Another significant drawback in interpreting the accuracy of observed values is the complete lack of studies of the xenon effect in tissues that have undergone pathologic changes. We do not know if tissue such as that seen in ischemia, tumor, or a seizure focus responds to xenon in the same fashion as normal tissue.

The statistical techniques that have been said to validate the quantifiable aspects of xenon CT also should be questioned. Correlational statistics showing a rise in microsphere counts in animal models [14] or a rise in the flow of xenon-133 [15] coupled with a rise in calculated xenon CT values are not the same as saying that a calculated blood flow of 50

ml/100 g/min in microsphere or ^{133}Xe methods is reflected as a flow of 50 ml/100 g/min by xenon CT. A rise from 40 ml/100 g/min to 50 ml/100 g/min when one technique is used and a rise from 60 ml/100 g/min to 75 ml/100 g/min when the other technique is used will be reflected as a strongly positive correlation. However, if one value is true, then the other is necessarily false. In animal studies, multiple sampling of small numbers of subjects often are used in the evaluations, thus understating potential differences between subjects. Because of the many limitations with xenon CT scanning, I doubt the reliability of flow values it provides. Higher standards should be required before a technique is called quantifiable.

The performance of a xenon CT scan involves repeated scanning of the same brain slices during the administration of xenon. A minimum of five scans is performed through the same tissue over 5–7 min. For acetazolamide testing, this sequence must be repeated, meaning at least 10 CT slices through the same tissue in a single sitting. If xenon CT scans with acetazolamide testing are to be performed serially before, during, and after repeated embolization procedures, radiation doses should be considered. Certainly, patients who have many arteriograms and embolizations and other diagnostic CT scans already are receiving significant irradiation to the head.

The effects of the administration of 25–30% xenon on mental status should not be discounted. Calculations of blood flow are based on superimposition of scans that are obtained throughout the administration of xenon, and CT density calculations are compared from one scan to the next. Therefore, the patient must remain motionless throughout the study. A tight-fitting gas mask must be placed over the patient's mouth and nose such that no air leak is present in order to maximize xenon concentration and provide accurate determinations of expiratory gas for CBF calculation and monitoring of the patient. These technical limitations inhibit patients' tolerance and can limit the accuracy of the numerical values obtained from the images. Many patients will not tolerate the testing, as evidenced by the 20% failure rate in the study by Tarr et al. [1]. This conforms to my experience also.

Though it probably is not accurate enough to be considered truly quantifiable, I do not dispute the literature showing correlation between xenon CT flow images and CBF in normal brain tissue or the demonstration of flow defects in hypoperfused areas. However, if xenon CT scanning is not truly quantifiable, it must be compared with those other techniques that are, admittedly, qualitative. This includes technetium or iodoamphetamine single-photon emission CT (SPECT). Xenon CT could have advantages in sensitivity over SPECT with ^{99m}Tc-HMPAO or iodoamphetamine. Statistically valid comparative studies are lacking. The clinical relevance of any demonstrated increased sensitivity also would need to be proved. It is hoped that future comparisons will be able to include MR perfusion imaging. With SPECT, the patient is given an IV injection of the radionuclide. In the case of ^{99m}Tc-HMPAO, the images can be acquired any time within approximately 24 hr and will reflect the flow that existed at the time of injection. My colleagues and I have found this technique particularly helpful during temporary carotid occlusion testing, as it saves transporting the patient to the brain-blood-flow imaging device while the balloon is still inflated in the carotid artery. Its simplicity and lack of discomfort lead to high tolerance by patients and rare failure to acquire a study. Because the acquisition is three-dimensional and without skip areas in the brain, coronal, sagittal, and axial images can be formatted. Use of a dual isotope technique permits simultaneous baseline acquisition and acetazolamide testing with this technology as well (Fig. 1) but requires a device with the ability to separate ^{123}I and ^{99m}Tc peak energies.

The development of MR perfusion imaging is promising and should lead to higher resolution without exposure to radiation. The ability to administer radionuclides in sites remote from the imaging device will remain an advantage of SPECT relative to MR or CT, although the coupling of flow imaging with anatomic imaging may make MR perfusion imaging more convenient in many situations.

Both positron emission tomography and ^{133}Xe imaging allow quantifiable determination of CBF. The expense and questionable reimbursement for positron emission tomography and the poor resolution in ^{133}Xe imaging remain disadvantages in those techniques.

Debate over which technology to use should not impede acceptance of the benefit of CBF imaging. My colleagues and I use it routinely in identification of seizure foci, in Alzheimer disease, in various psychiatric disorders, and in management of occlusive cerebrovascular disease. It helps predict tolerance of carotid sacrifice, as mentioned before. Furthermore, the physiologic information supplied can lead to insights about neuronal function or about diseases under investigation that may be understood fully only over time and with observations in multiple centers.

Future studies of CBF imaging in interventional procedures should help define the situations in which it is or is not helpful in therapeutic decision making. An inherently complementary relationship exists between the ability to image CBF and the ability to halt or increase regional arterial supply.

The existence of increased flow after embolization of an AVM is interesting but does not necessarily mean resection should be delayed. Further investigation is needed, for instance, to resolve whether it could indicate the patient who is at risk for delayed hemorrhage from embolization, and in whom surgery should be performed sooner. This seems unlikely, but this type of question will be resolved only by the disciplined study of larger numbers of patients and with appropriate clinical follow-up.

With the possibility of using cerebral angioplasty in the treatment of atherosclerotic disease or of vasospasm after subarachnoid hemorrhage, we are confronted with the dilemma of determining which patients are candidates for therapy. Again, diagnostic ability to identify a population at risk and definition of therapeutic effect may be an application of CBF imaging [16].

Because CT or MR cannot show edema resulting from stroke until 12–24 hr after the stroke, their usefulness in early decision making in that setting is limited to exclusion of hemorrhage or other processes that may contraindicate in-

tervention. CBF imaging can show a defect immediately. Physiological imaging therefore may help us understand the timing and effect of thrombolytic therapy as such therapy becomes used more widely in acute stroke.

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