EDITORIAL

Cerebral Versus Myocardial Stress Perfusion Imaging: Role of Pharmacological Intervention in the Diagnostic Assessment of Flow Reserve

Radionuclide imaging and semiquantitation of rCBF by SPECT using a number of radiotracers have been shown to be potentially useful in the management of patients with cerebrovascular disease (CVD). In this issue of the *Journal*, two interesting papers by Oku et al. (*1*) and Hoshi et al. (*2*) study the clinical utility of cerebral SPECT imaging with pharmacological intervention to assess cerebrovascular flow reserve in patients with chronic ischemic CVD and in patients with moyamoya disease.

Oku et al. (*1*) observed that in patients with chronic ischemic CVD, ^{99m}Tc-HMPAO SPECT with CO_2 inhalation showed a 10% increase in ^{99m}Tc-HMPAO uptake in patients without any major artery obstruction and a 6% increase in patients with regions supplied by carotid arteries with major obstruction. The difference in the two groups was considered significant enough to conclude that compromised cerebral perfusion reserve is seen in patients with obstructed major cerebral artery disease. The authors also concluded that this technique should be useful in clinical management. The authors used a double-dose technique of sequential imaging with the subject in the same position, which, after image subtraction, allowed interventional imaging to be accomplished in the same imaging session along with quantification.

Hoshi et al. (*2*) evaluated the effect of acetazolamide on rCBF using ^{123}I-IMP in patients with moyamoya disease. Moyamoya disease consists of an obstruction of the terminal internal carotid artery with collateral formation in the form of a mesh of fine blood vessels (hence its name "puff of smoke") located in multiple regions, particularly that of the basal ganglia. Symptoms arise due to intracerebral and subarachnoid hemorrhage and recurrent cerebral infarction. In a group of six patients who had sequential rest and interventional imaging, the authors observed decreased flow in the upper and lower frontal, parietal and temporal lobes in patients with grade 2 and 3 moyamoya disease. The results were not expressed as percent change in blood flow, but as a cerebral-to-cerebellar ratio. With acetazolamide, patients with grade 2 but not grade 1 moyamoya disease showed a significant decrease in the cerebral-to-cerebellar ratio in corresponding regions. Patients with grade 3 disease did not show a significant decrease in the cerebral-to-cerebellar ratio but instead showed abnormalities at rest. Hoshi et al.'s results suggest a consistent relationship of rest/stress imaging characteristics with the severity of angiographically documented disease.

Most cerebral SPECT perfusion studies are performed under resting conditions. The results, however, reflect the presence of damage to brain tissue that has already occurred, or cerebral blood flow that is significantly compromised at rest. Most cerebrovascular disease is silent, until the disease, usually atherosclerotic disease, has progressed to critical stenosis not compensated by collateral circulation under some or all hemodynamic conditions, or until at least one growing lesion has become unstable and a focus for occlusive thrombosis or the source of embolic material. Significant effort has been expended by many investigators to evaluate the clinical usefulness of cerebrovascular vasodilation using pharmacological intervention with agents that induce changes in brain perfusion. Any method that increases rCBF by pharmacological or physiological means would be expected to enhance the clinical usefulness of cerebral perfusion imaging in the assessment of cerebral perfusion reserve by uncovering cerebrovascular disease not detected by imaging at rest.

Stress cerebrovascular imaging is similar in principle to routine myocardial stress perfusion imaging performed with exercise or pharmacological intervention. With the recent introduction of several brain perfusion imaging agents, it was hoped that cerebrovascular perfusion imaging would find a position analogous to myocardial perfusion imaging in routine clinical management. The end result has been a mixture of development of its actual potential and continued wishful thinking.

Successful stress testing in either the brain or the heart is dependent on four requirements. First, a suitable radiotracer must be available. In myocardial perfusion imaging, ^{201}Tl and ^{99m}Tc-labeled sestamibi or teboroxime exhibit reasonably linear uptake with flow up to several times that of resting flow before leveling off at high flow rates. For cerebrovascular imaging, ^{133}Xe and ^{123}I-IMP appear to possess good linearity at normal resting flow ratios. However, ^{99m}Tc-labeled HMPAO and ECD have been shown to have nonlinear uptake properties even at resting flow rates (low by cardiovascular standards), resulting in lessened contrast of flow differentiation despite the superior imaging quality characteristics of these two tracers.

The second prerequisite is inducing sufficient vasodilatation to unmask hemodynamically significant vascular lesions. The success of myocardial perfusion stress imaging was helped by the ability of the myocardium to produce and safely tolerate a large in-

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crease in blood flow by increasing demand by work-loading or by vasodilation. Exercise can increase myocardial flow two to three times the resting levels. Although exercise can produce significant myocardial ischemia as frequently as 50% of the time in patients with suspected coronary artery disease, it is tolerated with acceptable safety, despite its duration from several minutes to 30 min. In coronary vasodilation, blood flow increases of 300%–400% are well tolerated, with clinically evident ischemia presenting about 10%–15% of the time due to combined increased demand and vasodilator steal phenomenon. This has helped to ensure high sensitivity for detection of individual vessel disease of 50%–80% with an overall sensitivity of 80%–90%. The final result is good diagnostic and prognostic capability in long-term prospects, after myocardial infarction but before noncardiac surgery and following intervention.

By contrast, intense mental effort only modestly increases large vessel cerebral blood flow. Because physiological intervention does not radically change cerebral blood flow, one must resort to pharmacological intervention. Although myocardial ischemia is well tolerated and safe enough to be documented by ECG and imaging methods, the same does not necessarily apply for cerebral imaging, where ischemia produces neurological functional deficits and possible loss of consciousness. Clearly, such side effects would be less readily accepted by patients than induced angina. Unless this limitation could be circumvented by well controlled short-acting cerebral vasodilators and appropriate monitoring, cerebrovascular stress imaging will not be as successful as myocardial stress imaging.

The mechanisms of coronary vasodilatation produced by dipyridamole and adenosine are closely related, of relatively short duration and are readily reversed, but unfortunately these agents do not produce effective cerebrovascular dilatation. Carbon dioxide (CO_2) inhalation or acetozolamide administration play analogous roles with related mechanisms, in that CO_2 inhalation produces vasodilatation of short duration (continuous inhalation is required) and is potentially well tolerated. Vasodilatation induced by acetazolamide, which inhibits carbonic anhydrase, lasts for longer periods of time and has limited potential for dose titration and reversibility.

The increase in rCBF with acetazolamide is reportedly about 30% when ^{133}Xe is the tracer (*3*) and 10%–30% when ^{99m}Tc-HMPAO is used (*4,5*). In a review article by Yudd et al. (*6*), the reported range of blood flow increase with acetazolamide was 5%–70%. When compared with myocardial imaging, this range is quite small. Dingler et al. (*7*) studied patients with CVD who did or did not receive acetazolamide, and reported an increase in sensitivity from 45% to 85% over rest imaging. The increase in rCBF with inhalation of 5% CO_2 and PET imaging resulted in an increase of flow up to 25% (*8*), whereas other studies measured increases of 17%–68% (*9*). The limitations of weak stressor agents and possibly a low contrast imaging agent help explain the low sensitivity for detection of significant (>70%) stenosis by Oku et al. in only 11 of 30 patients. One can argue that CO_2 inhalation or acetazolamide administration do not allow for measurement of cerebrovascular reserve if the vascular tree is not maximally stressed. This is analagous to the limitations of low-level exercise or suboptimal drug dosage in myocardial stress imaging. Another limitation is the presence of generous cerebrovascular collaterals via the Circle of Willis.

If this technique cannot detect the majority of patients with significant stenoses, then its use as a reliable diagnostic tool for cerebrovascular stenosis is precluded. Its clinical use of these procedures is limited to the most hemodynamically severe disease. Its clinical use would be compelling if there was reliable prognostic information in patients with positive studies, with benefits to be derived in terms of enhanced survival from intervention. This point emphasizes the third requirement for successful cerebral stress perfusion imaging: the availability of interventional or therapeutic modalities which affect symptoms, morbidity or survival. This still remains to be documented in large clinical trials. Endarterectomy is performed principally in patients with symptomatic carotid obstruction, which is investigated angiographically. With its low diagnostic sensitivity, cerebrovascular perfusion imaging could not replace angiography or carotid ultrasound studies in the investigation of symptomatic patients. The treatment of asymptomatic bruits, and for that matter asymptomatic vascular obstruction that might be revealed by noninvasive screening, is controversial. Routine extracranial-intracranial bypass surgery was not found to prevent ischemic strokes in atherosclerotic disease (*10,11*), which helps explain the lack of wide acceptance for radionuclide cerebrovascular imaging among clinicians or institutions as an essential step in patient management.

Lastly, the final component for successful imaging is the technique's ability to provide unique and essential information not readily available from other competing diagnostic modalities. This is not the case for cerebrovascular perfusion imaging in view of the availability of other noninvasive means, such as Doppler ultrasound, digital contrast angiography and MRI, which are routinely used to assess the presence and severity of cerebrovascular obstruction. There is no doubt that cerebrovascular perfusion imaging provides functional information not provided by the other modalities on the hemodynamic significance of vascular lesions and affected territories, but its impact on patient management is marginal.

The clinical utility of radionuclide imaging in moyamoya disease, found mainly in Japanese children and young adults, but is seen elsewhere and among older individuals as well, is dependent on the ability to diagnose the disease and follow its severity as an alternative to serial angiograms. Diagnosis is made by angiography, since the appearance of the disease on

perfusion brain scans is not specific. Although Hoshi et al. were able to correlate the resting image characteristics and response to acetazolamide with angiographic severity of disease, the role of vascular flow reserve in clinical management is unclear. Several possibilities are suggested. One possible role is documentation of disease progression. The necessity for serial follow-up presumes that clinical follow-up is insufficient and that cerebral perfusion imaging could substitute for other modalities following clinical deterioration. Because deterioration can occur in the form of intracerebral and subarachnoid hemorrhage and recurrent cerebral infarction, its differentiation cannot be performed without CT or angiographic studies. The real value of cerebral perfusion stress imaging lies in the potential of predicting ischemic stroke in jeopardized regions that correspond to grade 2 disease. This was suggested in a recent study of perfusion and vasodilatory reserve studied by an alternate method of serial rest/stress blood volume imaging (*12*) and is aided by the possibility of actual benefit from bypass surgery (*13,14*). The connection, however, between the demonstration of a defect in flow reserve and the prediction of ischemic events that could be prevented by intervention still needs elucidation. Though this condition is rare in the U.S., it can serve as a paradigm for other more common cerebrovascular disease states.

The most important factor in the acceptance and success of stress cerebrovascular perfusion imaging in CVD lies in the future availability of effective interventional therapy, i.e., in the form of medical therapy or revascularization for control of symptoms or improvement of prognosis. When compared to the aggressive interventional approach in coronary revascularization, cerebrovascular revascularization is of limited benefit, and acute revascularization or thrombolysis remain unproven modalities. In many ways, cerebrovascular imaging is a technique still in search of a reliable niche. Its limitations, the availability of competing diagnostic modalities and limited interventional avenues have frustrated universal adoption. Furthermore, its clinical utility will receive increasing critical scrutiny as rising cost concerns are debated worldwide, particularly in the U.S.

There are reasons, however, to view cerebrovascular stress imaging optimistically. There is considerable pressure to investigate more aggressive interventional approaches to acute stroke in the form of revascularization and thrombolysis, with the understanding that previous attempts were administered too late for the intervention to be effective. Just as the lack of effective therapy has hindered the application of cerebrovascular perfusion imaging, success in developing interventions would be expected to open new possibilities. It follows that brain perfusion imaging should be included in clinical interventional trials to a maximum degree and that more aggressive and effective cerebral vasodilators that can be administered safely should be developed.

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REFERENCES

1. Oku N, Matsumoto M, Hashikawa K, Moriwaki H, et al. Carbon dioxide reactivity by consecutive ^{99m}Tc-HMPAO SPECT in patients with chronically obstructed major cerebral artery. *J Nucl Med* 1994;35:32–40.
2. Hoshi H, Ohnishi T, Jinnouchi S, et al. Cerebral blood flow study in patients with moyamoya disease evaluated by IMP SPECT. *J Nucl Med* 1994;35:44–50.
3. Bonte F, Devous M, Reisch J. The effect of acetazolamide on regional blood flow in normal subjects as measured by single photon emission tomography. *Invest Radiol* 1988;23:564–568.
4. Matsuda H, Higashi S, Kinuya K, et al. SPECT evaluation of brain perfusion reserve by the acetazolamide test using Tc-99m-HMPAO. *Clin Nucl Med* 1991;16:572–579.
5. Burt RW, Witt RM, Cikrit DF, Venkata R. Carotid artery disease: evaluation with acetazolamide-enhanced Tc-99m-HMPAO SPECT. *Radiology* 1992;182:461–466.
6. Yudd AP, Van Heertum RL, Masdeu JC. Interventions and functional brain imaging. *Semin Nucl Med* 1991;21:153–158.
7. Dingler WH, Beil D, Deininger H-K. Tc-99m-HMPAO SPECT in patients with reversible CVD: comparison of sensitivity with and without acetazolamide (Diamox) [Abstract]. *J Nucl Med* 1990;31:789.
8. Levine RL, Sunderland JJ, Lagreze HL, Nickles RJ, Rowe BR, Turski PA. Cerebral perfusion reserve indexes determined by fluoromethane positron emission scanning. *Stroke* 1988;19:19–27.
9. Ringelstein EB, Eyck SV, Mertens I. Evaluation of cerebral vasomotor reactivity by various vasodilating stimuli: comparison of CO_2 to acetazolmide. *J Cereb Blood Flow Metab* 1992; 12:162–168.
10. The EC/IC Bypass Study Group. The international cooperative study of extracranial/intracranial arterial anastomosis (EC/IC bypass study): methodology and entry characteristics. *Stroke* 1985;16:397–406.
11. The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. *N Engl J Med* 1985; 313:1191–1200.
12. Inoue Y, Momose T, Machida K, et al. Cerebral vasodilatory capacity mapping using technetium-99m-DTPA-HSA SPECT and acetazolamide in moyamoya disease. *J Nucl Med* 1993; 34:1984–1986.
13. Karasawa J, Kikuchi H, Furuse S, et al. Treatment of moyamoya disease with STA-MCA anastomosis. *J Neurosurg* 1978;49:679–688.
14. Kobayashi H, Hayashi M, Handa Y, et al. EC-IC bypass for adult patients with moyamoya disease. *Neurol Res* 1991;13:113–116.