Use of Technetium-HMPAO To Demonstrate Changes in Cerebral Blood Flow Reserve Following Carotid Endarterectomy

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Cerebral perfusion through stenosed internal carotid arteries is usually maintained by autoregulation. However, flow reserve may be reduced, suggesting hemodynamically significant stenosis, and such reduction should be improved by carotid endarterectomy. This concept was studied in 20 subjects with unilateral internal carotid artery stenosis (major stenosis ≥ 70%, minor stenosis ≤ 50%). Thirteen had experienced recent transient ischemic attacks and seven had no definite focal symptoms. Subjects underwent Tc-HMPAO cerebral SPECT during acetazolamide dysautoregulation before and after internal carotid endarterectomy. Nine (45%) had perfusion defects that improved after surgery, suggesting surgery had improved cerebral flow reserve. Seven had defects that did not improve after surgery. Four had worsened or new defects after surgery, suggesting perioperative infarcts. The relatively large proportion of patients with improved cerebral blood flow reserve after surgery suggests that this technique may have a significant role to play in assessing which patients might benefit from carotid endarterectomy.

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Internal carotid artery stenoses are associated with strokes and transient ischemic attacks (TIAs). Cerebral embolism has been postulated to be the most common cause of cerebral ischemia associated with such lesions (reviewed in *1*). However the fact that patients can become symptomatic during hypotensive episodes suggests that internal carotid (ICA) lesions can be hemodynamically significant (*2–5*). Treatment for ICA stenoses includes carotid endarterectomy (CEA), which removes ulcerated plaques, a site of origin of emboli, and reduces luminal obstruction, making it a potential treatment for both causes of ischemia (*1,6*). Such treatment is often considered justified in symptomatic patients because of the frequency with which TIAs precede strokes, and in experienced units good results can be obtained (*1*). However, in patients with asymptomatic ICA stenoses, the role of surgery is more controversial (*6,7*). In both groups, if patients with hemodynamically significant stenoses could be identified and if it could be shown that the hemodynamic abnormality of such lesions responds to CEA, then better patient selection and improved surgical results might be obtained.

Under resting conditions, cerebral perfusion can be maintained by stenosed ICAs through the operation of cerebral autoregulation (*8–10*). This mechanism causes dilatation of resistance vessels distal to the stenosis and hence normalization of flow through the stenosed segment. Flow reserve in the territory supplied by these vessels, however, may be reduced (*10–13*), and in these patients, if hemodynamic conditions change (e.g., in systemic hypotension), the already dilated distal resistance vessels will be unable to dilate sufficiently and regional hypoperfusion will result. Symptoms of cerebral ischemia may follow (*9, 10,12*).

Stenoses that are causing reduced flow reserve should be identifiable by measuring cerebral perfusion after induction of cerebral dysautoregulation with either carbon dioxide inhalation or acetazolamide injection. These agents produce pharmacologic dilatation of cerebral resistance beds and hence a marked increase in blood flow through normal ICAs (*14–17*). However distal to significantly stenosed vessels, in regions supplied by inadequate collaterals, the resistance beds are already maximally or near maximally dilated and will be unable to dilate significantly. A differential in regional perfusion between the tissues supplied by these vessels and normal vessels will result, and this can be measured using an appropriate cerebral blood flow agent (*4,5,10,18–22*).

In patients who do have such hemodynamically significant lesions, it would be expected that CEA would reduce the risk of stroke, providing it did improve local cerebral flow reserve. Although the effect of CEA on cerebral autoregulation has been studied previously (*4,23*), such studies have tended to involve small numbers of subjects or to use methods of cerebral perfusion assessment that are not widely available. Technetium-HMPAO has been

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shown to be an adequate marker of cerebral perfusion under both physiologic and pathologic conditions (*24–30*) and during dysautoregulation (*16,31*) with safe dosimetry characteristics (*24,32,33*), thus allowing cerebral perfusion to be imaged with standard SPECT equipment. The current study used this agent to assess the changes in cerebral flow reserve following carotid endarterectomy. Patients with unilateral ICA stenosis were studied so that the cerebral hemisphere on the nonstenosed side could act as a control in each patient for the side on which surgery was performed.

METHODS

Patients

Patients were recruited on a voluntary basis from those with unilateral ICA stenosis who attended the vascular unit at this institution for carotid endarterectomy from 1987 to 1990. For the purposes of this study, unilateral stenosis was considered to be present if one ICA demonstrated a stenosis of at least 70% luminal narrowing, while the contralateral ICA was at most 50% stenosed. Patients with a history of previous stroke (defined as a neurologic deficit present for longer than 1 wk) and those with permanent neurologic signs were excluded.

Twenty-eight subjects were initially recruited. Eight were subsequently excluded: two had technically unsatisfactory cerebral perfusion studies because they were unable to tolerate the positioning required; one suffered a cerebral infarct prior to surgery; one suffered a perioperative cerebral hemorrhage; two failed to return for follow-up despite uncomplicated surgery; and two were found on review of their cerebral angiography to have carotid stenoses greater than 50% bilaterally.

Of the 20 patients included in this report, 11 were male and 9 were female, with an age range from 54 to 78 yr. Twelve had experienced TIAs attributable to the major ICA stenosis within 4 mo of the study, one (Patient 1) had experienced a contralateral TIA but because of angiography and oculoplethysmography results was proceeding to CEA of the major stenosis, and seven had no definite symptoms of focal ischemia. The clinical presentation for each patient is shown in Table 1.

Cerebral Perfusion Studies

After the nature of the procedure was fully explained to the patients, informed consent was obtained. A teflon cannula was inserted in a large antecubital or forearm vein and acetazolamide (500 mg) was administered intravenously. The patient was then positioned supine on a standard tomographic bed facing a rotating head analog gamma camera (GE 400 ACT, General Electric, Australia) fitted with a high-resolution parallel-hole collimator and interfaced with a computer (DEC PDP 11/34, Digital, Australia). The patient's head was positioned in a specially constructed radiolucent holder and held still by a velcro band. The lights were dimmed after positioning and subsequent interaction with the patient was held to a minimum.

Twenty-five minutes after injection of acetazolamide, at the time of maximal dysautoregulation (*14*), 500 MBq of Tc-labeled HMPAO (Ceretec, Amersham, Australia) was administered via the cannula as an intravenous bolus. An initial dynamic study was recorded. Fifteen minutes after initial injection of HMPAO a SPECT study of the head was acquired over 64 angles equally spaced through 360° with each angle being collected for 30 sec. This study was reconstructed using a Metz prefilter developed in-house (*34*) and standard NPS software (Philips, Australia).

The perfusion scans were assessed in two ways. First, standard transaxial, coronal, and sagittal sections were reconstructed and assessed subjectively and regions of relatively decreased perfusion (defects) were identified (Fig. 1A). Second, transaxial slices were used to construct "bull's-eye" maps of cerebral perfusion using a previously described method similar to that used in thallium tomography (*18,35*) (Fig. 2). Each scan was classified into one of four groups: normal; perfusion defect ipsilateral to the side of major ICA stenosis; bilateral defects; contralateral defects. The anatomical location of these defects was also noted.

Postoperative scans were performed identically to preoperative scans. The processing of these scans differed only in that a program was used during reconstruction to ensure that the orbitomeatal line was placed at the same angle as in the preoperative study. This enabled comparable slices to be reconstructed. These studies were then assessed in the same way as the preoperative studies, and the perfusion was graded as to whether it was improved, unchanged, or worse following surgery (Fig. 1B).

Cerebral Angiography and CT Scans

All patients had carotid angiography and cerebral CT scanning before and after CEA.

RESULTS

The results of carotid angiography and cerebral perfusion studies are shown in Table 1. A comparison of postoperative cerebral perfusion studies with preoperative studies is shown in Table 2.

Nine patients (45%) showed perfusion defects that improved after CEA. Eight of these had single defects ipsilateral to the side of major stenosis, and one had bilateral defects that improved after CEA. Of these nine patients, five had suffered recent TIAs, while four had experienced no focal ischemia.

Seven patients had perfusion defects that did not improve after surgery. Of these cases, only one had a single defect ipsilateral to the major stenosis, while three had bilateral defects and three had solitary contralateral defects.

One patient (Patient 12) had a perfusion defect that increased in size after surgery. Before surgery, the cerebral CT in this patient showed an ipsilateral lacunar infarct, and following surgery the CT showed a new contralateral lacune in the midbrain. Three patients who had normal cerebral perfusion studies before surgery showed new defects postoperatively, but all showed normal postoperative CT scans.

Abnormal CT scans were found in three patients despite absence of physical signs. Patient 12 has been discussed above. Preoperatively, Patient 6 showed a basal ganglia lacunar infarct contralateral to the side of CEA and had no change after surgery. Patient 16 had a normal CT prior to surgery, but postoperatively showed a new frontal infarct ipsilateral to the side of CEA.

All postoperative angiograms showed no residual ste-

TABLE 1
Clinical Presentation, Preoperative Carotid Angiography, Side of CEA, and Cerebral Perfusion Study Results for All Patients

Patient no.	Symptoms	ICA stenosis	CEA	Preoperative HMPAO defects	Postoperative HMPAO defects
1	L hemiparesis	70% Left 50% Right	Left	L temporal R parietal	No change
2	L arm paresis	99% Right Normal Left	Right	R occipital L parietal	No change
3	Left facial RIND	90% Right 40% Left	Right	R parietal L temporal	No change
4	R hemiparesis	70% Left Normal Right	Left	L temporoparietal	Improved
5	R arm paresis	90% Left 50% Right	Left	L parietal	No change
6	R arm paresis and R homo hemi	90% Left 50% Right	Left	L parietal	Improved
7	R visual field defect	80% Left 20% Right	Left	R occipital	No change
8	R amurosis fugax	95% Right Normal Left	Right	R frontoparietal	Improved
9	L amurosis fugax	90% Left 50% Right	Left	L parietal	Improved
10	R amurosis fugax	80% Right Normal Left	Right	Normal	Right parietal
11	R amurosis fugax	90% Right Normal Left	Right	Normal	Right occipital
12	Total blindness	90% Right Normal Left	Right	R occipitotemporal	Larger defect
13	Dysphasia	95% Left 10% Right	Left	L frontoparietal	Improved
14	Dizziness	70% Left 50% Right	Left	R hemisphere	No change
15	Dizziness	80% Right 20% Left	Right	R parietal	Improved
16	Asymptomatic	80% Left 20% Right	Left	L frontoparietal	Improved
17	Asymptomatic	80% Right Normal Left	Right	L frontoparietal	No change
18	Asymptomatic	95% Left 20% Right	Left	L parietal	Improved
19	Asymptomatic	90% Right 20% Left	Right	R parietal L parietal	Both improved
20	Asymptomatic	80% Right 20% Left	Right	Normal	R occipital L frontal

nosis on the side of surgery. On clinical examination after surgery, none of the patients, including those with worsened perfusion and those with CT scan abnormalities, had focal neurologic signs.

DISCUSSION

It has previously been shown that patients suffering from TIAs can have normal cerebral perfusion that becomes

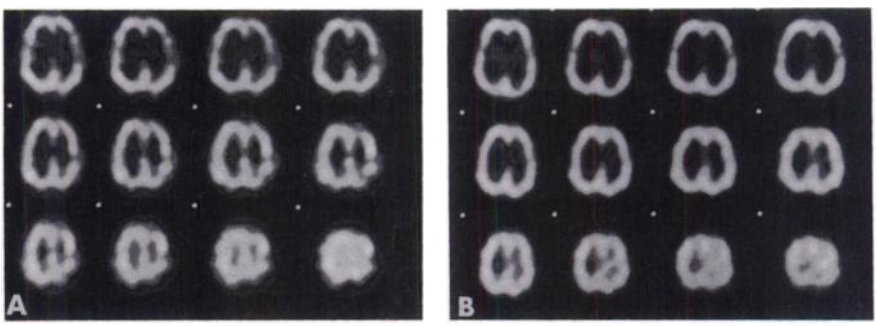

FIGURE 1. (A) Transaxial slices of preoperative perfusion study of a patient with left ICA stenosis (Patient 13). A left-sided defect is seen extending through a number of slices. (B) Similarly placed transaxial slices following carotid endarterectomy showing almost complete resolution of the previous defect.

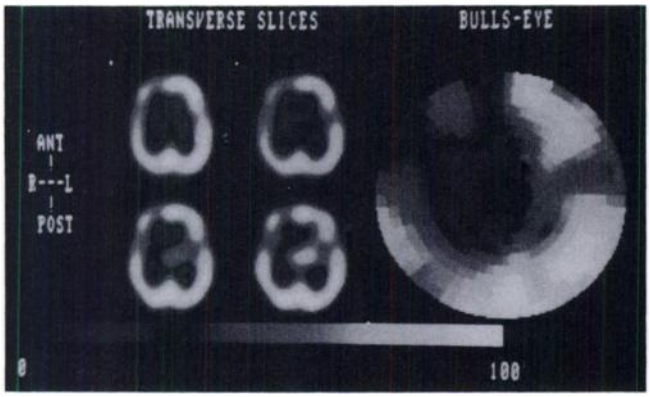

FIGURE 2. Four sample transaxial slices showing a large right frontoparietal perfusion defect and the corresponding bull's-eye map (Patient 8).

abnormal after cerebral dysautoregulation (*18–21*), and it is logical that this is also true for some patients with asymptomatic ICA stenoses. It seems likely that such abnormalities are caused by reduced cerebral blood flow reserve and are therefore associated with hemodynamically significant stenoses (*10,19,20*). If carotid endarterectomy is to reduce the hemodynamic significance of these lesions, it must produce improvement in autoregulation. Such improvement following carotid endarterectomy has been reported briefly (*4,23*), however no simple method that is widely available has been extensively used to investigate it.

The current study was designed to use Tc-HMPAO to assess the proportion of patients with unilateral ICA stenosis who have abnormalities in regional cerebral autoregulation that can be improved by CEA. These abnormalities were identified as perfusion defects that improved after surgery and were found in 45% of the patients studied. This was true for patients with recent TIAs and for those without a history of focal ischemia. In eight of these cases, the perfusion abnormality was ipsilateral to the major ICA stenosis, while the ninth patient had bilateral defects which both improved. These results suggest that in these nine cases the ICA stenoses themselves were causing impaired cerebral blood flow reserve that was amenable to CEA.

Seven patients had preoperative perfusion defects that did not improve after CEA, and there are a number of possible explanations for such abnormalities. Only one of these patients (Patient 5) showed a single perfusion defect ipsilateral to the side of major stenosis. Postoperative CT scan in this patient was normal and the angiogram showed no residual stenosis on the side of surgery. This defect may represent a fixed perfusion defect related to the recent TIAs (*22,36*), but whether it would ultimately resolve, or whether it represents permanent damage despite a normal cerebral CT scan is not clear. Three patients had contralateral defects that failed to improve after surgery. Patient 17 had a defect in a site compatible with a reversible ischemic neurologic deficit (RIND) 14 yr previously despite absence of current physical signs. The others had no obvious explanation in their clinical history, raising the possibility of subclinical strokes. The three patients with bilateral defects all had normal CT scans, and these abnormalities carry the same implications as the other four defects which failed to improve.

Another possible explanation for defects that fail to improve also exists. Cerebral atherosclerosis is not a disease localized to the level of the proximal ICA. Intracranial disease also may be present, although it can be difficult to identify on standard angiography. If there is distal disease, correcting the proximal ICA stenosis may not significantly alter the regional autoregulation intracranially. The current study was not designed to preoperatively differentiate this group of patients from those whose abnormalities are due to their ICA stenosis alone. To identify these subgroups, it would be necessary to perform cerebral perfusion studies with and without dysautoregulation before and after CEA. This approach would also identify patients with inducible perfusion abnormalities preoperatively that are present at rest after surgery, a combination suggesting perioperative infarction.

Four patients had new or enlarged perfusion defects after surgery. In only one of these was the new defect associated with a CT scan abnormality, suggesting that the incidence of subclinical cerebral infarction related to CEA is higher than that estimated by CT scanning alone (*37, 38*).

The concept of hemodynamically significant ICA stenoses being those that cause reduced cerebral blood flow reserve, and therefore are identifiable by examining cerebral perfusion during dysautoregulation, is not new (*4–6, 19–22*), but no simple method using widely available technology has been developed to show the proportion of such abnormalities that can be successfully treated with carotid endarterectomy. In the current study, the combination of acetazolamide and cerebral Tc-HMPAO distribution imaged with a standard rotating head gamma camera was used to demonstrate reduction in cerebral flow reserve, which improved after CEA in 45% of selected patients with unilateral ICA stenosis. These results suggest that this technique, or a variation of it, may have a significant role to play in the selection of patients who will benefit from CEA.

TABLE 2
Comparison of Postoperative Cerebral Perfusion Studies with Preoperative Studies

Pre-CEA Perfusion result	Post-CEA Perfusion		
	Improved	No change	Worse
Ipsilateral defect	8	1	1
Contralateral defect	0	3	0
Bilateral defects	1	3	0
Normal	0	0	3

REFERENCES

1. Lord RSA. *Surgery of occlusive cerebrovascular disease.* St Louis: CV Mosby; 1987.
2. Sand BJ, Rose HB, Barker WF. Effect of cardiac dysrhythmia on cerebral perfusion. *Arch Surg* 1976;111:787.
3. Ruff RL, Talman WT, Petito F. Transient ischaemic attacks associated with hypotension in hypertensive patients with carotid artery stenosis. *Stroke* 1981;12:353–355.
4. Takagi Y, Hata T, Ishitobi K, et al. Cerebral blood flow and CO2 reactivity before and after carotid endarterectomy. *Acta Neurol Scand* 1979;60:506–507.
5. Tsuda Y, Kimura K, Yoneda S, et al. Cerebral blood flow and CO2 reactivity in transient ischaemic attacks: comparison between TIAs due to the ICA occlusion and ICA mild stenosis. *Neurol Res* 1983;5:17–37.
6. Gates PC. Asymptomatic carotid stenosis: a review. *Aust NZ J Med* 1986;16:817–821.
7. Quinones-Baldrich WJ, Moore WS. Asymptomatic carotid stenosis: rationale for management. *Arch Neurol* 1985;42:378–382.
8. Brice JG, Dowsett DJ, Lowe RD. Haemodynamic effects of carotid artery stenosis. *Br Med J* 1964;5421:1363–1366.
9. Mendelow AD, Graham DI, Tuor UI, et al. The haemodynamic effects of internal carotid artery stenosis and occlusion. *J Neurosurg* 1987;66:755–763.
10. Vorstrup S. Tomographic cerebral blood flow measurements in patients with ischaemic cerebrovascular disease and evaluation of the vasodilatory capacity by the acetazolamide test. *Acta Neurol Scand* 1988;114(suppl):1–48.
11. Kanno I, Uemura K, Higano S, et al. Oxygen extraction fraction at maximally vasodilated tissue in the ischaemic brain estimated from the regional CO2 responsiveness measured by positron emission tomography. *J Cereb Blood Flow Metab* 1988;8:227–235.
12. Frackowiak RSJ. Pathophysiology of human cerebral ischaemia: studies with positron tomography and oxygen-15. In: Sokoloff L, ed. *Brain imaging and brain function. Research publications: Association for Research in Nervous and Mental Disease, volume 63.* New York: Raven Press; 1985:139–161.
13. Powers WJ, Fox PT, Raichle ME. The effect of carotid artery disease on the cerebrovascular response to physiologic stimulation. *Neurology* 1988; 38:1475–1478.
14. Hauge A, Nicolaysen G, Thoresen M. Acute effects of acetazolamide on cerebral blood flow in man. *Acta Physiol Scand* 1983;117:233–239.
15. Vorstrup S, Henrikson L, Paulson OB. Effect of acetazolamide on cerebral blood flow and cerebral metabolic rate for oxygen. *J Clin Invest* 1984;74:1634–1639.
16. Devous MD, Payne JK, Lowe JL. Extraction, retention and kinetics of Tc-ECD and HMPAO following intracarotid injection in cynomolgus monkeys [Abstract]. *J Nucl Med* 1989;30:742.
17. Bonte FJ, Devous MD, Reisch JS. The effect of acetazolamide on regional cerebral blood flow in normal human subjects as measured by single-photon emission computed tomography. *Invest Radiol* 1988;23:564–568.
18. Lord RSA, Yeates M, Fernandes V, et al. Cerebral perfusion defects, dysautoregulation and carotid stenosis. *J Cardiovasc Surg* 1988;29:670–675.
19. Keyeux A, Laterre C, Beckers C. Resting and hypercapnic rCBF in patients with unilateral occlusive disease of the internal carotid artery. *J Nucl Med* 1988;29:311–319.
20. Vorstrup S, Boysen G, Brun B, et al. Evaluation of the regional cerebral vasodilatory capacity before carotid endarterectomy by the acetazolamide test. *Neurol Res* 1987;9:10–18.
21. Burt RW, Reddy RV, Mock BM, et al. Acetazolamide enhancement of HIPDM brain flow distribution imaging. *J Nucl Med* 1986;27:1627–1631.
22. Kassiotis P, Steinling M. Le debit sanguin cerebral local et sa reactivite a l'acetazolamide dans les accidents ischemiques transitoires. *Rev Neurol (Paris)* 1987;143:806–813.
23. Vorstrup S, Engel H, Lindewald H, et al. Haemodynamically significant stenosis of the internal carotid artery treated with carotid endarterectomy. Case report. *J Neurosurg* 1984;60:1070–1075.
24. Holmes RA, Chaplin SB, Royston KG, et al. Cerebral uptake and retention of ^{99m}Tc-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO). *Nucl Med Commun* 1985;6:443–447.
25. Neirinckx RD, Canning LR, Piper IA, et al. Technetium-99m-d,l-HMPAO: a new radiopharmaceutical for SPECT imaging of cerebral blood perfusion. *J Nucl Med* 1987;28:191–202.
26. Leonard J, Nowotnik DP, Neirinckx RD. Technetium-99m-d,l-HMPAO: a new radiopharmaceutical for imaging regional brain perfusion using SPECT—a comparison with iodine-123-HIPDM. *J Nucl Med* 1986; 27:1819–1823.
27. Lear JL. Tc-99m-HMPAO as a tracer for LCBF: evaluation using quantitative triple label digital autoradiography [Abstract]. *J Nucl Med* 1987; 28:559.
28. Andersen AR, Friberg H, Lassen NA, et al. Serial studies of cerebral blood flow using ^{99m}Tc-HMPAO: a comparison with ^{133}Xe. *Nucl Med Commun* 1987;8:549–557.
29. Bartolini A, Gasparetto B, Bacigalupo F, et al. Single photon emission computed tomography with technetium-99m-hexamethyl propylenamine oxime in the clinical assessment of cerebral ischaemia. *Eur J Neurol* 1988;28:232–235.
30. Spreafico G, Cammelli F, Gadola G, et al. Luxury perfusion in cerebral vascular disease evaluated with technetium-99m-HMPAO. *Clin Nucl Med* 1987;12:217–218.
31. Ell PJ, Jarritt PH, Costa DC, et al. Functional imaging of the brain. *Semin Nucl Med* 1987;17:214–229.
32. Nowotnik DP, Canning LR, Cumming SA, et al. Development of a ^{99m}Tc-labelled radiopharmaceutical for cerebral blood flow imaging. *Nucl Med Commun* 1987;6:429–431.
33. Deckart H, Ertl S, Blottner A, et al. Radiopharmacokinetics and radiation dose from ^{99m}Tc-HM-PAO (preliminary report). *Eur J Nucl Med* 1987;13:429–431.
34. McGee K, Eberl S, Walker P, et al. A comparison of two-dimensional prefiltering techniques for single photon computed tomography (SPECT) studies. *Aust NZ J Med* 1988;18(suppl):500.
35. Hille N, Eberl S, Duncan A, et al. Quantitation of relative regional cerebral perfusion. *Aust NZ J Med* 1987;17(suppl):474.
36. D'Addato M, Pedrini L, Stella A, et al. Carotid endarterectomy. Pre- and post-operative monitoring with cerebral SPECT. *Int Angiol* 1988;7:234–237.
37. Berguer R, Sieggreen MY, Lazo A, et al. The silent brain infarct in carotid surgery. *J Vasc Surg* 1986;3:442–447.
38. Sise MG, Sedwitz MM, Rowley WR, et al. Prospective analysis of carotid endarterectomy and silent cerebral infarction in 97 patients. *Stroke* 1989;20:329–332.