The value of acetazolamide single photon emission computed tomography scans in the preoperative evaluation of asymptomatic critical carotid stenosis

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Purpose: Acetazolamide (ACZ)-enhanced single photon emission computed tomography (SPECT) scans can assess both cerebral perfusion and vascular reactivity. Patients with asymptomatic critical carotid artery stenosis were evaluated for cerebral vascular reactivity to determine the effect of extracranial occlusive disease and the effect of carotid endarterectomy (CEA) on intracerebral reactivity.
Methods: In 44 patients with asymptomatic critical carotid artery stenosis, cerebral perfusion and vascular reactivity were assessed before CEA with resting and ACZ-enhanced SPECT scans. All patients had a 70% or greater ipsilateral internal carotid artery stenosis. Preoperative ACZ-enhanced SPECT scans were obtained, usually 5 days before CEA. Postoperative ACZ-enhanced SPECT scans were obtained in 30 patients.
Results: Preoperative SPECT scans were asymmetric, revealing focal (n = 19) or global (n = 15) decreased reactivity in 34 patients (77%). Ten patients had symmetric or normal reactivity. After CEA, 23 patients demonstrated an improvement in reactivity ipsilateral to the side of surgery. The remaining seven patients failed to improve after surgery.
Conclusion: Although all patients had a high-grade internal carotid stenosis, nearly a quarter of the patients had excellent intracerebral collateral flow. Only 71% of patients demonstrated improved intracerebral vasoreactivity after CEA. The lack of improvement in the other patients may have resulted from intracerebral pathology or lack of improvement in the extracranial carotid hemodynamics. (J Vasc Surg 1999;30:599-605.)

Single photon emission computed tomography (SPECT) can be used to assess regional cerebral blood flow by using lipophilic radiopharmaceutical agents that cross the intact blood-brain barrier. Changes in the uptake and retention of the radiopharmaceutical agent is a reflection of regional cerebral blood flow.[1,2] Decreased perfusion suggests an insufficient collateral network and a dependence on the ipsilateral carotid.

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In addition, cerebral blood flow functional reserve or lack of reserve can be assessed by means of the SPECT scan through the use of the drug acetazolamide (ACZ).[1,3] The brain's normal cerebral autoregulatory capabilities result in vessel dilation when reduced cerebral perfusion occurs. Eventually, however, when maximal vasodilation occurs, compensation can no longer occur, placing that area of brain tissue at risk should perfusion diminish further. Before maximal vasodilation, the brain's autoregulatory capabilities mask the critical nature of any diminished cerebral blood flow seen on the resting SPECT scan. The administration of ACZ is a means of helping to assess perfusion reserve by demonstrating the hemispheric response to this cerebral vasodilator. Normally, ACZ increases cerebral blood flow by as much as 80%.[4] After ACZ administration, a SPECT scan by which minimal or no increase in hemispheric or focal intensity (reactivity) is demonstrated suggests that this portion of the brain with decreased reactivity is at risk

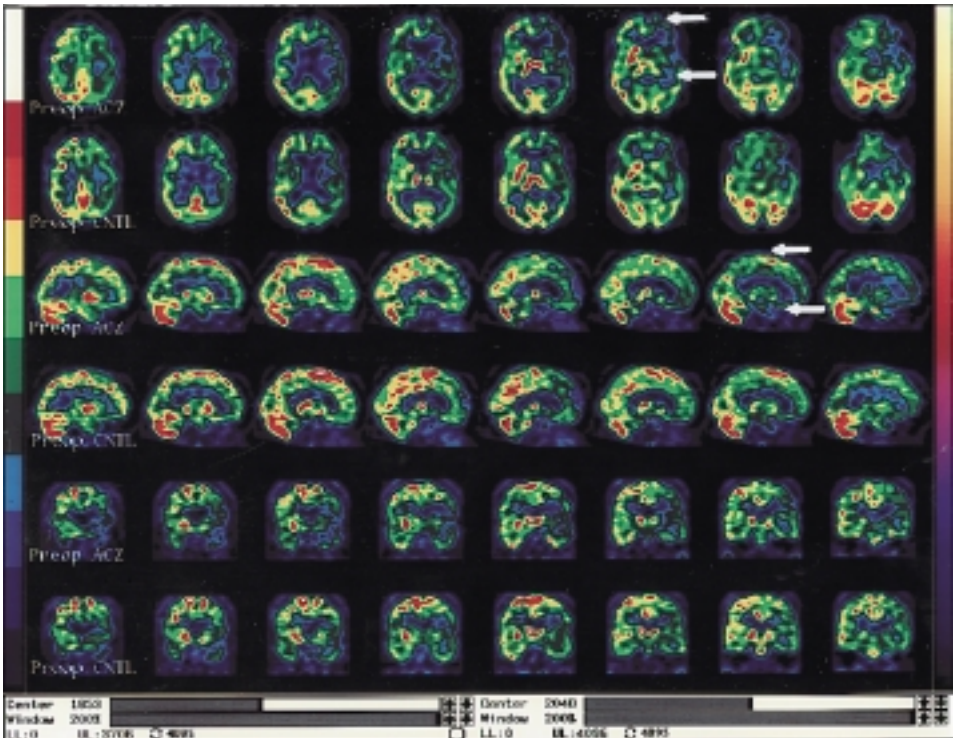

Fig 1. The transverse, sagittal, and coronal views of the preoperative single photon emission computed tomography (SPECT) scan of an asymptomatic patient with a high-grade internal carotid stenosis. *Rows 1, 3, and 5* comprise the acetazolamide-enhanced SPECT scan, whereas *rows 2, 4, and 6* are images of the corresponding resting SPECT scan. Perfusion (*rows 2, 4, and 6*) is decreased in the frontal parietal area. Reactivity is also decreased in a similar area and seen between the *arrows* in *rows 1, 3, and 5* on the acetazolamide-enhanced SPECT scan.

for stroke if cerebral blood flow further diminishes.[5] The ACZ-enhanced SPECT scan functions as a stress study. This is similar to the Persantine thallium scan of the heart.

This retrospective study evaluated resting and stress (ACZ-enhanced) SPECT scans performed in asymptomatic patients with critical internal carotid artery stenosis (more than 70% stenosis) before and after carotid endarterectomy (CEA) was evaluated to determine the effect of extracerebral carotid blood flow on intracerebral perfusion and reactivity and to determine the effect of CEA on intracerebral vascular reactivity.

PATIENTS AND METHODS

In 44 patients with asymptomatic critical internal carotid artery stenosis, cerebral perfusion and vascular reactivity were assessed before CEA with ACZ-enhanced SPECT scanning. This study was conducted at the Richard L. Roudebush Veteran's Administration Hospital in Indianapolis, Ind, and all patients were men. The mean age at the time of surgery was 68 years (range, 56 to 81 years). All patients were asymptomatic from the ipsilateral carotid stenosis (mean, 89%). Seven patients had a history of stroke in the remote past (more than 2 years). Eight patients had undergone a CEA on the contralateral side, whereas one patient had an ipsilateral CEA. Thirty-six patients had a history of smoking, and 14 patients still smoked. Thirty-one patients had hypertension, and 15 patients had diabetes mellitus, four of whom required insulin. Only three patients had a history of hyperlipidemia. Twenty-eight patients had a history of coronary artery disease.

Preoperative examination included a carotid duplex scan and arch with four-vessel angiography in all 44 patients. Other diagnostic tests were left to the discretion of the physician examining the patient preoperatively and the surgeons observing the patient after surgery. Computerized axial tomography (CT scan) of the brain was obtained in 37 patients preoperatively. All patients had both a rest-

ing and stress (ACZ-enhanced) SPECT scan preoperatively. The SPECT studies were performed from 1 to 27 days before CEA (mean, 5.11 ± 5.34 days).

All patients were studied with a technetium-enhanced 99m (^{99m}Tc), hexamethyl propylene amine oxine (HMPAO) SPECT scan (Ceretec, Medi+ Physics, Heights, Ill). HMPAO is a radiopharmaceutical that crosses the intact blood-brain barrier. ACZ (1 g; Diamox, Lederal Lab Division, Pearl River, NY) was administered intravenously 20 minutes before the intravenous injection of HMPAO (30mCi^{99m}Tc) in a quiet area of the imaging suite. Patients were required to lie quietly while undergoing the SPECT imaging study. SPECT scans, with and without ACZ, were obtained 6 hours and preferably 24 hours apart. These were usually obtained the week before surgery (mean, 5.11 ± 5.34 days). Sagittal, coronal, and transverse images were obtained (Fig 1). The SPECT imaging studies were performed and interpreted by two staff physicians from the section of nuclear medicine who were not aware of the patient's specific clinical history.

A Siemens "rainbow" (Siemens Medical Systems, Iselin, NJ) was used to display the images. Normal flow will fall within the top 20% of the color display and is demonstrated as white or red. The next 10% is displayed as yellow, and the next 10% is displayed as shades of green. Abnormal flow is defined as any area below the 30% level. Therefore, normal flow is seen as red, white, or yellow. An abnormal perfusion pattern is suggested by means of an asymmetric uptake between hemispheres or within comparable regions of the hemispheres. Very poor perfusion is demonstrated as purple, whereas an infarct will appear black. After the administration of ACZ, decreased or complete lack of perfusion reserve is demonstrated by means of greater contrast or asymmetry developing between the hemispheres or corresponding regions within the cerebral hemispheres. Complete details of the method for SPECT imaging and its interpretation have been described previously.[1,3,4] Images were evaluated for hemispheric uptake, symmetry, focal or regional decreases in uptake, and the response to ACZ in scans in which this drug was administered.

In brief, a scan is interpreted as "normal" when symmetrical uptake exists throughout the brain and falls in the top 30% of the SPECT color display (white, red, or yellow) and when no qualitative change occurs in distribution between the control and ACZ-enhanced scan (category A). A state of "compromised perfusion reserve" is defined by means of normal distribution on the control study, with focal or hemispheric asymmetry after ACZ administration (category B). "Chronic ischemia with compromised perfusion reserve" is defined as hemispheric or focal asymmetry that is more severe (greater contrast or larger area) after ACZ administration (category C; Fig 2). The final category is seen when areas of the brain with decreased resting flow demonstrate a normal symmetric stress scan and suggest a loss of selective neuronal differentiation or loss of cerebral blood flow autoregulation (category D). An infarction is demonstrated by means of severely decreased focal uptake, usually below 60% of maximum, appearing black on the color display, with no change after ACZ administration.[3]

All surgery was performed by four board-certified vascular surgeons. A primary closure of the vessel was performed in 31 cases, whereas a patch angioplasty was used for the other 13 cases. ACZ-enhanced SPECT scans were obtained in 30 patients, at a mean of 43 ± 5 days postoperatively. These were obtained at the discretion of the physicians who observed the patients postoperatively. Carotid duplex examination was performed at the patients' first postoperative vascular surgery clinic visit, which was usually scheduled 4 to 6 weeks after surgery. One patient was lost to follow-up and never had a postoperative duplex examination.

RESULTS

Before operation, by means of angiographic criteria, the ipsilateral internal carotid artery had at least a 90% stenosis in 27 patients, an 80% to 89% stenosis in 14 patients, and a 70% to 79% stenosis in four patients. The contralateral carotid was occluded in three patients, had a 90% to 99% stenosis in one patient, an 80% to 89% stenosis in one patient, a 70% to 79% stenosis in one patient, a 60% to 69% stenosis in two patients, and a 50% to 59% stenosis in nine patients. The remaining 28 patients had less than a 50% narrowing of the contralateral carotid artery. The internal carotid artery mean stenosis was 89% and 39% for the ipsilateral and contralateral carotid arteries, respectively. Cerebral cross filling was evident on angiographic examination in 14 patients. In all except three patients, the direction of crossfill was directed toward the hemisphere under study. In the remaining three patients, who had a contralateral occlusion, crossfill was directed toward the side of the occlusion.

By means of the preoperative CT scans obtained in 37 patients, an earlier cerebral infarction was demonstrated in eight and four patients in the ipsilateral and contralateral hemispheres, respectively. Additionally, in six and eight patients, ipsilateral and contralateral lacunar infarctions were noted.

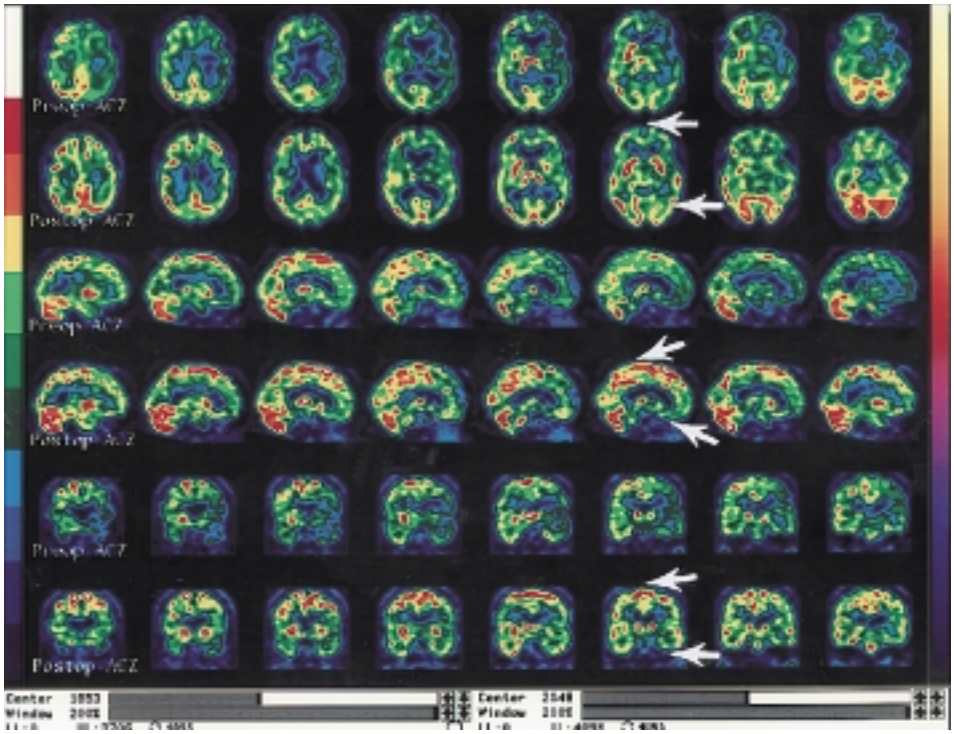

Fig 2. The preoperative acetazolamide-enhanced single photon emission computed tomography (SPECT) scan images are seen in *rows 1, 3, and 5*. The corresponding postoperative acetazolamide-enhanced SPECT scan images are seen in *rows 2, 4, and 6*. After carotid endarterectomy, markedly improved reactivity is evident between the *arrows* in *rows 2, 4, and 6*. The images are for the same patient as in Fig 1.

Decreased perfusion to the ipsilateral cerebral hemisphere was demonstrated in 30 patients (68%) by means of preoperative resting SPECT scans (n = 44). In eight patients, this was a global phenomenon, whereas in the other 22 patients, it involved only a portion of the ipsilateral hemisphere. Fourteen patients had a normal perfusion study. Thirty-four of the 44 patients (77%) who underwent an ACZ-enhanced SPECT scan before CEA had a lack of or markedly decreased ipsilateral cerebral vascular reactivity. This was a global effect in 15 patients and focal in the other patients. Cerebral reactivity or evidence of vasodilatory reserve was present in 10 patients. Decreased contralateral perfusion was evident in 15 patients (33%). Thirteen patients had a focal deficit, whereas the deficit was global in two patients. Contralateral reactivity was diminished or absent in 14 patients (32%), a finding that was global in four patients and focal in the other patients (Table I). Ipsilateral infarcts were demonstrated by means of five SPECT scans. Contralateral infarcts were noted in two SPECT scans. Old infarctions were not detected by means of SPECT scans as well as they were by means of a good quality CT scan.

There were no deaths and no new cerebral events after surgery. A normal, patent ipsilateral vessel was confirmed by means of a carotid duplex examination performed at the first postoperative vascular clinic visit (4 to 6 weeks postoperatively) in all patients, except one patient who had an ipsilateral occlusion. One patient was lost to follow-up and did not undergo this examination.

ACZ-enhanced SPECT scans were obtained in 30 patients after a mean of 43 ± 5 days postoperatively. Improved ipsilateral cerebral vasoreactivity was demonstrated in 17 cases (71%). In seven patients, cerebral reactivity was still diminished after CEA. Contralateral cerebral vasoreactivity was normal and remained unchanged postoperatively in 19 patients (63%). Decreased contralateral vasoreactivity persisted postoperatively in nine patients (Table I). Two patients with decreased contralateral reactivity improved after CEA.

Of the seven patients who did not demonstrate ipsilateral improvement after CEA, one had an occluded ipsilateral carotid before the SPECT scan. This was an incidental finding on his first postoper-

TABLE I. Preoperative and postoperative cerebral perfusion and reactivity

	Preoperative (n = 44)		*Postoperative (n = 30)*	
Cerebral blood flow	*Ipsilateral*	*Contralateral*	*Ipsilateral*	*Contralateral*
Normal perfusion	14	29	–	–
Decreased perfusion	30 (68%)	15 (33%)	–	–
Focal	22	13	–	–
Global	8	2	–	–
Normal reactivity	10	30	23* (71%)	21 (70%)
Decreased reactivity	34 (77%)	14 (32%)	7†	9†
Focal	19	10		
Global	15	4		

*17 improved / six unchanged from preoperative normal.
†Unchanged from decreased preoperative flow.

TABLE II. Categoric assessment of both perfusion and reactivity

	Preoperative ipsilateral rCBF				*Postoperative ipsilateral reactivity*		
Category	*Perfusion*	*Reactivity*	*n*	*%*	*n*	*Impro or NL*	*Unimproved*
A	NL	NL	5	11%	4	4	0
B	NL	↓	9	20%	7	6 (71%)	1
C	↓	↓	25	57%	17	11 (65%)	6
D	↓	NL	5	11%	2	2	
Totals			44		30	23 (71%)	7

rCBF, Regional cerebral blood flow; *Impro,* improved; *NL,* normal; ↓, decreased.

ative duplex study. Another patient was lost to follow-up after postoperative SPECT scanning. He never returned for a carotid duplex study and may have represented another subclinical postoperative carotid occlusion. No obvious explanation could be found in the remaining five patients for this lack of improvement, other than possible intracerebral vascular disease.

For an optimal classification of preoperative cerebral blood flow based on a functional assessment, both perfusion (baseline or resting SPECT scan) and reactivity (ACZ-enhanced or stress SPECT scan) were considered. Only five patients (11%) had a "normal" (category A) study. Nine patients (20%) demonstrated a "compromised perfusion reserve" (category B). "Chronic ischemia with a compromised perfusion reserve" (category C) was observed in 25 patients (57%). Five patients (11%) had lost their ability to autoregulate cerebral perfusion (category D). Thirty of these 44 patients underwent a postoperative ACZ-enhanced SPECT scan. Four patients in category A, seven patients in category B, 17 patients in category C, and two patients in category D underwent ACZ-enhanced SPECT scans postoperatively. The patients in category A had maintained normal reactivity postoperatively. Seventy-one percent (n = 6) of patients in category B and 65% (n = 11) of patients in category C demonstrated normal or improved cerebral reactivity postoperatively. The two patients in category D continued to demonstrate normal postoperative cerebral reactivity (Table II).

DISCUSSION

The anatomical basis of cerebral blood flow is well established by means of both carotid duplex evaluation and cerebral angiography. The functional effect is less well understood.[6] Through the use of various radiopharmaceutical agents, regional cerebral blood flow can be assessed by means of SPECT scans. Cerebral vasodilators, such as CO_2 or ACZ, can be used to assess the reactivity or perfusion reserve still available.[1-3] This method serves as a means of assessing hemispheric collateral flow and vasodilatory capacity or perfusion reserve. The value of cerebral SPECT scans, in general, appears to be the ability to image regional intracerebral blood flow and to assess vascular reactivity through the use of cerebral vasodilators.

The predictive value of cerebral blood flow studies and reactivity is best demonstrated by Webster et al[5], who measured cerebral blood flow with stable

xenon computed tomography both at baseline and after a vasodilatory challenge with ACZ in 95 symptomatic patients who had a 70% or greater ipsilateral stenosis or occlusion. Patients did not undergo surgical repair for various reasons, but were actively observed. Patients were stratified into two groups: group 1 demonstrated no more than a 5% decrease in flow in any vascular territory, whereas group 2 demonstrated greater than a 5% decrease in flow. In follow-up, significantly ($P < .0005$) more patients in group 2 experienced a new stroke. This data demonstrates that the loss of cerebral reactivity in patients with severe internal carotid stenosis is an important predictor of stroke in symptomatic patients.[5]

Several studies of primarily symptomatic patients with internal carotid artery stenosis have demonstrated decreased ipsilateral perfusion or reactivity in 70% to 100% of the patients by means of preoperative resting SPECT scans.[2,7-10] In our earlier study of 64 symptomatic and asymptomatic patients, decreased reactivity was demonstrated in 78% of the patients by means of ACZ-enhanced SPECT scans.[6] Most recently, Tawes and Lull,[11] in an excellent study, examined 74 patients preoperatively and postoperatively with ACZ-enhanced SPECT scans. Only 10 patients were asymptomatic. Sixty-five percent of patients demonstrated decreased ipsilateral perfusion on preoperative examination. In our present study of asymptomatic patients, which includes the 25 patients from our earlier study, decreased reactivity was demonstrated in 77% of the patients. This is similar to other studies of primarily symptomatic patients.

The value of SPECT scans is in the functional assessment of regional cerebral blood flow, which is accomplished best by combining the results of the resting and the ACZ-enhanced SPECT scan. Patients in category A (five of our patients) have excellent collateral flow, which is evidenced by means of normal perfusion and good vasodilatory capacity, as evident from normal reactivity studies. Autoregulation appeared to be intact. These patients would appear to represent the lowest risk for an adverse event should the ipsilateral carotid occlude, as long as no other emboli or distal thrombosis occurred. They still have vasodilatory reserve with which to compensate.[3] Although these five patients may have tolerated a complete internal carotid occlusion and are at low risk for a hypoperfusion stroke, they are obviously still at risk for an embolic stroke.

Patients in category B (nine of our patients) have poor collateral flow. Any compensation for the critical internal carotid stenosis is through maximal vasodilation. If collaterals were adequate, then maximal vasodilation would not have occurred.[3] These patients would certainly be at risk should flow diminish even further, because their cerebral circulation is already at maximal vasodilation and there is no longer any functional reserve.

Patients in category C (23 of our patients) have poor collateral flow and maximal vasodilation that is not currently adequate to compensate for the decreased perfusion status. These patients have exceeded their autoregulatory capabilities and lack collateral flow.[3] Any further loss of flow could easily result in an adverse cerebral event. The implications of the SPECT scan, however, are not 100%, because one of these patients had an occluded ipsilateral carotid artery postoperatively and had diminished reactivity, but did not have a stroke.

Patients in category D are perhaps the most interesting. These patients have good vasoreactivity but decreased perfusion. There were only five of these patients in our study. The decreased perfusion seen in those patients suggests that they lack adequate collaterals. The decreased perfusion also suggests that they should be maximally vasodilated to compensate for the poor perfusion, but patients in category D are not maximally vasodilated, as evidenced by their response to ACZ. For unclear reasons, they have lost their ability to autoregulate cerebral blood flow. Although they can still vasodilate, it is not in an appropriate manner. Decreased perfusion would normally be the impetus for maximal vasodilation. This did not occur in patients in category D. An earlier infarction or loss of neuronal tissue from atrophy may have contributed to this loss of autoregulatory ability. The hemisphere may no longer be able to sense the need for vasodilation, or decreased hemispheric consumption of oxygen may block the need for vasodilation.

Although some investigators have reported that all patients have improved reactivity after CEA, most investigators have noted an improvement in 64% to 78% of patients. This is similar to our rate, with 71% of patients demonstrating improved reactivity after CEA. Failure to improve perfusion or reactivity after CEA may result from failure to improve the flow dynamics of the ipsilateral carotid artery, such as from a postoperative carotid occlusion or stenosis of the affected side. Intracerebral small vessel disease may be a contributor to the unimproved vasoreactivity. Neuronal loss caused by atrophy or stroke may also result in little improvement in perfusion or reactivity after surgery.

In conclusion, this study of asymptomatic patients with ACZ-enhanced SPECT scans demon-

strates that 77% of the patients have decreased preoperative reactivity, suggesting both poor collaterals and maximal vasodilation with no vascular reserve. Although excellent collaterals were present in 23% of the patients, the potential for embolic stroke remains, and these patients should be offered CEA. Decreased cerebral perfusion / reactivity did not improve postoperatively in 23% of the patients, and in most cases, this appeared to be caused by intracranial pathology.

The value of ACZ-enhanced SPECT scans is as a means of detecting cerebral perfusion and reactivity and demonstrating the return of reactivity after CEA. Although this is of interest, most strokes are embolic in nature, and patients should be offered CEA regardless of the results of their SPECT scan.

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