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Brain SPECT with Dipyridamole Stress to Evaluate Cerebral Blood Flow Reserve in Carotid Artery Disease

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This is a preliminary study of SPECT brain scan using dipyridamole as a stress agent to assess cerebral blood flow reserve in six patients with severe carotid artery disease. **Methods:** We performed SPECT scanning of the brain, with and without dipyridamole stress. Dipyridamole (0.57 mg/kg) was given intravenously 3 min before infusion of ^{99m}Tc-HMPAO. Patients were studied 30 min later using a rotating head gamma camera. The scans were analyzed qualitatively and semiquantitatively. An acetazolamide stress SPECT image was also obtained in two patients. **Results:** All patients had at least 80% stenosis in one internal carotid artery, three of them also had contralateral carotid stenosis. The dipyridamole SPECT showed an increased region of hypoperfusion in the hemisphere ipsilateral to the severe carotid disease in four patients. That suggests poor perfusion reserve and the potential risk of regional ischemia. In four of six patients, side-to-side asymmetry increased from the baseline condition after injection of dipyridamole. The asymmetry index increased more after dipyridamole than after acetazolamide injection in two patients. **Conclusion:** This study suggests that dipyridamole stress SPECT is useful in assessing cerebral blood flow reserve. It demonstrates the region of poor vascular reserve in patients with severe carotid artery disease. Dipyridamole SPECT scans show more extensive hypoperfusion than acetazolamide in the two cases.

Key Words: SPECT; brain; dipyridamole; acetazolamide

J Nucl Med 1996; 37:1595–1599

Received Jun. 28, 1995; revision accepted Jan. 28, 1996.

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TABLE 1
Summary of Clinical and Carotid Angiographic Findings in Six Patients with Severe Carotid Artery Disease

Patient no.	Age (yr)	Sex	Presenting symptoms	Diagnosis and CT	Carotid artery (% of stenosis)
1	68	M	Syncope & Rt hemiparesis	Border zone infarction between Lt ACA and MCA	LICA 90%
2	72	M	Episodes of TIAs	Amaurosis fugax, Rt (normal CT)	RICA 95% LICA 60%
3	69	M	Rt hemiparesis and hemisensory deficit	Capsulo-striatal infarction, Lt	LICA 95% RICA 60% RICA 60%
4	63	M	Paresthesia	Border zone infarction, Rt frontal Lacuna, Lt periventricular	RICA 90% LICA 80%
5	76	M	Lt hemiparesis after a syncope (G-I bleeding)	Border zone infarction, Rt frontal Lacuna, Lt thalamus and corona radiata	RICA occlusion LICA 30%
6	52	M	Lt eye blindness	Lt central retinal artery occlusion (normal CT)	LICA 80%

ICA = internal carotid artery; MCA = middle cerebral artery; ACA = anterior cerebral artery; R = right; L = left.

Cerebral perfusion in the distribution of a stenotic internal carotid artery is usually maintained by autoregulation (*1*). The blood flow reserve in the territory supplied by the stenotic vessels may be reduced if hemodynamic conditions change (e.g., systemic hypotension).

Reduced blow flow reserve due to stenosis may be measured by cerebral perfusion after induction of cerebral dysautoregulation with either carbon dioxide inhalation or acetazolamide injection (*2*). These agents produce pharmacologic dilatation of cerebral resistance vessels. Thus, an increase in blood flow through normal intracranial arteries occurs. Resistance vessels are already maximally or near maximally dilated and will be unable to undergo additional dilation (*3,4*) in distal to significantly stenosed vessels, especially in the regions supplied by inadequate collaterals. The decreased brain perfusion reserve in patients with carotid artery stenosis indicates the reduced regional perfusion pressure and poor collateral circulation. That may predispose patients to risks of cerebral ischemia (*1,4*) or ischemic infarction, particularly watershed infarction (*5*), at a time of such stress as systemic hypotension or further narrowing of the internal carotid artery. Dipyridamole is an adenosine (a potent vasodilator) uptake inhibitor (*6*) and may increase blood flow in normal cerebral, coronary and peripheral vessels (*7–9*). It has been used as a vasodilating agent for ^{201}Tl SPECT cardiac imaging in assessing myocardial perfusion and ischemia in patients with suspected or known coronary artery disease who are unable to exercise (*10*). We report a preliminary study of brain SPECT imaging using dipyridamole as an alternative stress agent in six patients with severe internal carotid artery stenosis.

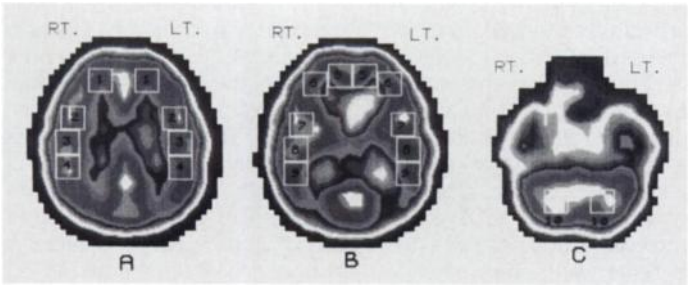

FIGURE 1. Squared ROI (20 pixels and 64 × 64 matrix resolution) in three transaxial planes. (A) Section through centrum semiovale. (B) Section through thalamus. (C) Section through cerebellum. ROI: (1) superior lateral frontal; (2) anterior parietal; (3) middle parietal; (4) posterior parietal; (5) mesial frontal; (6) inferior lateral frontal; (7) anterior temporal; (8) middle temporal; (9) posterior temporal; (10) cerebellum.

MATERIALS AND METHODS

Six patients (age 52–76 yr) with cerebral ischemic infarction, central retinal artery occlusion, amaurosis fugax or transient cerebral ischemia due to carotid artery disease were studied. A cardiac source of cerebral embolization and other etiologies of ischemic infarction were excluded by appropriate work-ups. Each patient underwent brain CT, cerebral arteriography and brain SPECT with and without dipyridamole stress. The clinical data are summarized in Table 1.

SPECT scans were obtained under resting conditions with the patients eyes open and ears unplugged without any acoustic, visual or motor stimulation. Both baseline and dipyridamole SPECT scans were obtained under similar environmental conditions. The dipyridamole SPECT scan was performed 1–3 days after the baseline study. Dipyridamole was given intravenously at a dose of 0.57 mg/kg over 4 min followed 3 min later by administration of 20 mCi ^{99m}Tc-HMPAO. Blood pressure, heart rate and EKG were monitored 2 min before the start of the test and continued until 20 min after dipyridamole administration. Patients were scanned 30 min after injection of ^{99m}Tc-HMPAO using a rotating gamma camera. The camera heads were equipped with low-energy, all-purpose collimators. Sixty-four projections with an imaging time of 35 sec per projection were obtained. After attenuation correction, 8.8-mm thick cross-sections were reconstructed as transaxial, coronal and sagittal views by backprojection and use of a Butterworth filter in 64 × 64 matrices.

Additionally, three-dimensional color tomograms were qualitatively assessed by a radiologist and a neurologist blinded to the patients' history and CT scan findings. The SPECT images were evaluated for focal or regional decreases in tracer uptake, hemispheric uptake symmetry and response to dipyridamole. Abnormal or asymmetric distribution includes any area below the top 30% level of uptake or a clearly different or diminished uptake in a hemisphere or region. The study showing worsening of focal or hemispheric asymmetry or hypoperfusion after dipyridamole administration was interpreted as compromised perfusion reserve. A semiquantitative method was also used to evaluate tracer uptake. A set of multiple square regions of interest (ROIs) (20 pixels in each

TABLE 2
Qualitative Interpretation of SPECT Scan Under Baseline Condition, Dipyridamole and Acetazolamide Stress

Patient no.	Carotid angio (% of stenosis)	Baseline hypoperfusion	Dipyridamole stress*	Acetazolamide stress*
1	LICA 90%	Lt MCA	Worsening of perfusion in Lt MCA	N/A
2	RICA 95% LICA 60%	Lt temporal and bilateral posterior parietal	Worsening of perfusion in both hemispheres	Worsening of perfusion in Rt MCA
3	LICA 95% RICA 60%	Lt MCA	Worsening of perfusion in Lt MCA	N/A
4	RICA 90% LICA 80%	Lt hemisphere and Rt parietal	No significant change	N/A
5	RICA 100% LICA 30%	Both hemispheres, Lt more than Rt	No significant change	N/A
6	LICA 80%	Lt temporal	Marked worsening of perfusion in Lt MCA	Minimal worsening of perfusion in Lt MCA

* Relative perfusion change to the baseline study. MCA = middle cerebral artery distribution.

ROI) were placed in the cortical ribbon over two supratentorial axial planes (through the centrum semiovale and thalamus level) and in one cerebellar plane. Three representative ROIs for the frontal, temporal and parietal lobes on each side were defined as shown in the Figure 1. ROIs were calculated as gamma counts per pixel. The cerebellar ROIs were used as a reference since there was no perfusion abnormality in the cerebellum of the study patients. The side-to-side asymmetry [asymmetry index] of tracer uptake between the regions distal to the carotid stenosis (or the side with more severe carotid artery disease) and the contralateral normal (or relatively normal) regions was calculated as follows:

(average counts per pixel in hypoperfused hemisphere) − (average counts per pixel in normal or relatively normal contralateral hemisphere)/(average counts per pixel in normal or relatively normal contralateral hemisphere).

The ROI/cerebellum was defined as follows:

ROI/cerebellum = (average counts per pixel of the ROIs of one hemisphere)/(average counts per pixel of right and left cerebellar ROIs).

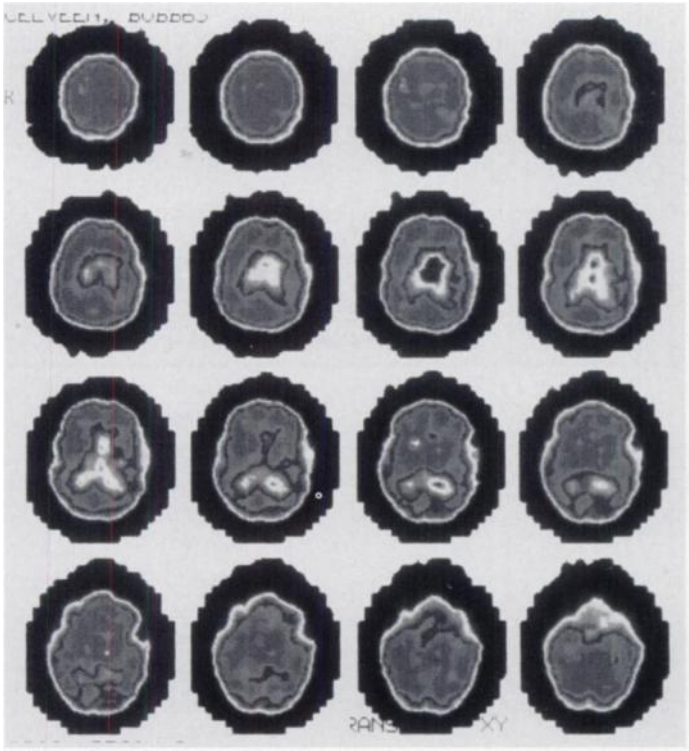

FIGURE 2. Baseline SPECT scan of brain on Patient 6 (transaxial view). The black-white illustration was developed from the color picture. Mild hypoperfusion is seen in the left parietal-temporal and left basal ganglia region.

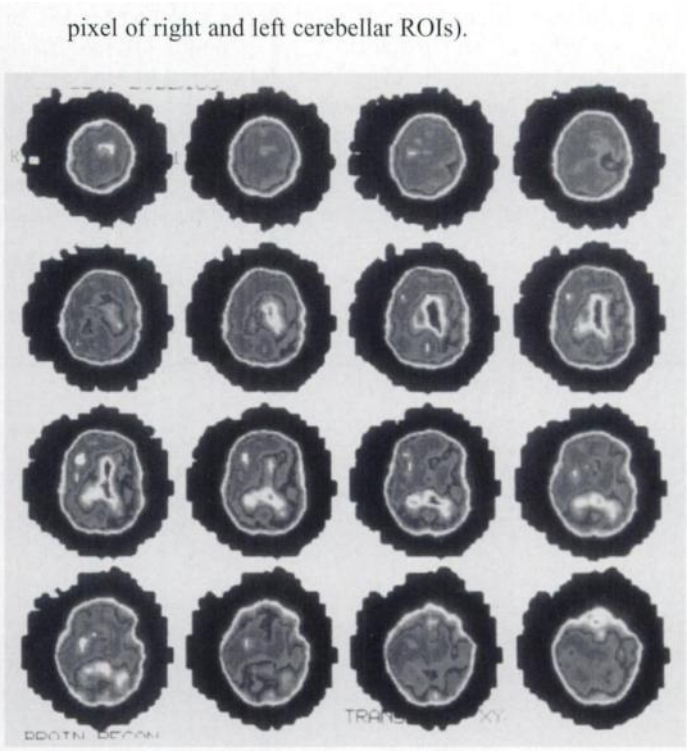

FIGURE 3. Acetazolamide-stress SPECT scan of brain on Patient 6 (transaxial view). In comparison with the baseline study, the slightly larger area of hypoperfusion is seen in the same area.

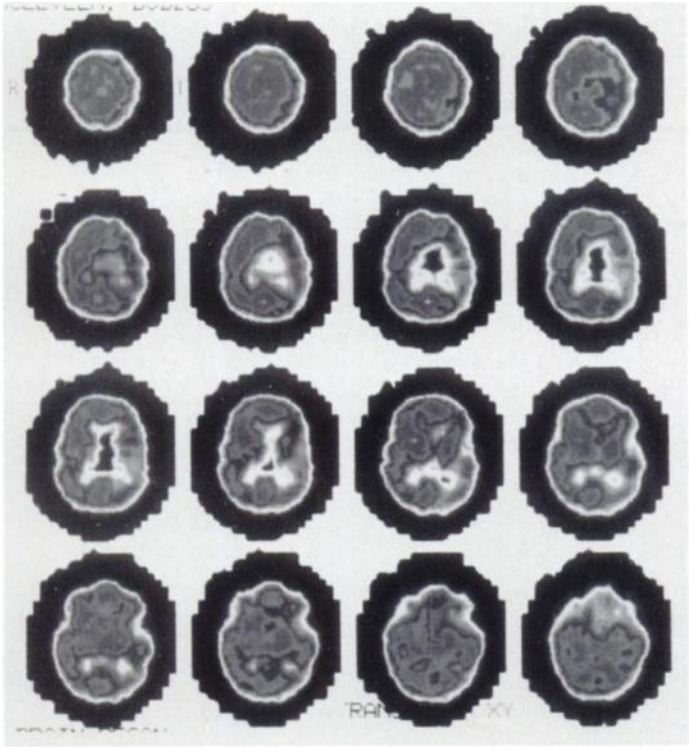

FIGURE 4. Dipyridamole-stress SPECT scan of brain on Patient 6 (transaxial view). Marked hypoperfusion is seen in the left cerebral hemisphere.

For comparison, an acetazolamide stress SPECT scan was also obtained for Patients 2 and 6. Acetazolamide (1 g) was given intravenously 25 min before the injection of ^{99m}Tc-HMPAO.

RESULTS

As shown in Table 1, each patient had at least 80% stenosis or occlusion of one internal carotid artery, three of them also had significant contralateral carotid stenosis (60% stenosis in two and 80% in one patient). Three patients suffered from border zone infarcts, one capsulostriatal infarction, one amaurosis fugax and another one central retinal artery occlusion. The baseline SPECT scans showed different degrees of hypoperfusion in the hemispheres ipsilateral to the internal carotid artery disease. The dipyridamole SPECT showed worsening of perfusion in the hemisphere or middle cerebral artery (MCA) distribution ipsilateral to the severe carotid artery disease in comparison to the baseline SPECT in four patients (Patients 1, 2, 3 and 6) (Table 2). This suggested poor cerebral perfusion reserve and the potential risk of regional ischemia. In two patients (Patients 4 and 5), no significant change of the perfusion pattern before and after the dipyridamole injection was demonstrated. Patient 2 had bilateral carotid artery disease, and an increased area of hypoperfusion was only seen in the right MCA distribution after acetazolamide stress and in both cerebral hemispheres after dipyridamole stress. Patient 6 had a left internal carotid artery stenosis (80%) and an old lacunar infarction in the anterior limb of left internal capsule. The baseline SPECT scan showed decreased perfusion in left basal ganglia area and left parietal-temporal region. The perfusion became minimally worse in left MCA distribution after acetazolamide injection, and even more extensive with dipyridamole stress (Figs. 2, 3 and 4).

The semiquantitative analysis showed an increased asymmetry index in the cerebral hemisphere ipsilateral to the severe carotid artery disease in four of six patients (Table 3). The asymmetry index ratio between dipyridamole stress and baseline, which represents the degree of perfusion decline, increased range from 112% to 429%. The ROI/cerebellum showed a lower ratio on the side with severe carotid artery disease, (except Patients 2 and 5) under baseline condition. With dipyridamole stress, the ROI-to-cerebellum ratio became lower on the side with severe carotid stenosis in all six patients. In Patients 2 and 5, the hemispheric perfusion appeared to decline on the side with the less stenotic carotid artery under basal conditions, and the diminished perfusion shifted to the side of more severe carotid disease under dipyridamole infusion. For Patient 6, the asymmetry index changed from −0.119 to −0.133 under dipyridamole stress and there was no change with acetazolamide stress (Figs. 2, 3, 4). The ROI-to-cerebellum ratio also demonstrated a decreased ratio on the left side (0.743 versus 0.848 on baseline; 0.657 versus 0.758 under dipyridamole stress) (Table 3).

TABLE 3
Asymmetry Index and ROI/Cerebellum Under Baseline Condition, Dipyridamole and Acetazolamide Stress

		Asymmetry index (AI)					ROI/Cerebellum	
Patient no.	Carotid angio (% of stenosis)	AI formula	Baseline	DPD	ACZ	AI ratio DPD/Baseline	Baseline	DPD
1	LICA 90%	$\frac{Lt-Rt}{Rt}$	−0.057	−0.079		139%	Lt 0.915	0.698
							Rt 0.983	0.775
2	RICA 95%	$\frac{Rt-Lt}{Lt}$	+0.013	−0.068	−0.050		Rt 0.736	0.576
	LICA 60%						Lt 0.710	0.623
3	LICA 95%	$\frac{Lt-Rt}{Rt}$	−0.077	−0.330		429%	Lt 0.876	0.682
	RICA 60%						Rt 0.957	0.832
4	RICA 90%	$\frac{Rt-Lt}{Lt}$	−0.050	−0.084		168%	Rt 0.810	0.834
	LICA 80%						Lt 0.855	0.925
5	RICA 100%	$\frac{Rt-Lt}{Lt}$	+0.068	−0.106			Rt 0.733	0.759
	LICA 30%						Lt 0.701	0.808
6	LICA 80%	$\frac{Lt-Rt}{Rt}$	−0.119	−0.133	−0.119	112%	Lt 0.743	0.657
							Rt 0.848	0.758

DPD = dipyridamole stress; ACZ = acetazolamide stress; LICA = left internal carotid artery; RICA = right internal carotid artery.

DISCUSSION

Dipyridamole is an adenosine uptake inhibitor (*6*), which is a potent vasodilator in most vascular beds and may induce arterial hypotension (*8,9*). The peak vasodilating effect of intravenous administered dipyridamole is found 6 min after the infusion, with a mean 9-bpm increase in heart rate and a mean 12-mmHg decrease in systolic blood pressure. The effect lasts for 10 min (*11*). We administered ^{99m}Tc-HMPAO for a SPECT study during the peak action of the dipyridamole. The study of dipyridamole in the dog model has demonstrated a reduction of mean arterial pressure of 20%, reduction in peripheral vascular resistance of 31%, blood flow increase in the left ventricle of 213% and decrease in cerebrovascular resistance of 21% (*8*). It appears that the peripheral vascular effect is more prominent than the cerebral vascular effect. In the rabbit model, however, cerebral blood flow increased (*12*).

The usefulness of evaluating cerebrovascular reserve and perfusion change with ^{99m}Tc-HMPAO SPECT after acetazolamide has been well demonstrated (*13*) in patients with carotid artery disease. The present study shows that dipyridamole can be used as a vasodilating agent to assess the cerebral blood flow reserve. After injection of dipyridamole, perfusion in the hemisphere ipsilateral to the severe carotid artery stenosis diminished in four of six patients. This may reflect a relatively ischemic area or hemodynamically compromised area showing intracranial steal phenomenon, which shifts flow from an ischemic area to the normal area. Decreased peripheral vascular resistance caused by dipyridamole may further enhance cerebral hypoperfusion. That dipyridamole is a strong cerebral vasodilating agent is also demonstrated by the increased ratio of the asymmetry index between dipyridamole stress and baseline, ranging from 112% to 429%. No significant perfusion change after dipyridamole injection suggests adequate cerebral perfusion reserve and collateral circulation. It is also possible that the patients were nonresponders to dipyridamole. Acetazolamide SPECT was performed in only two patients. Dipyridamole stress produced more perfusion changes than acetazolamide, both qualitatively and based on the Asymmetry Index. Whether the dipyridamole SPECT scan more reliably demonstrates adverse risk of cerebral ischemia in systemic hypotension requires further study. Some methodological problems deserve mention. Qualitative interpretation of a SPECT scan is subjective, particularly for those patients with subtle or mild abnormalities. The measurement of the representative ROIs is more objective but may not always reflect uptake in the entire hemisphere or lobes. In Patient 4, there was no significant change with and without dipyridamole stress by qualitative reading, but the asymmetry index indicated decline of the perfusion up to 168% after dipyridamole injection.

CONCLUSION

There were no complications in this study. The vasodilatory effect of intravenous dipyridamole on coronary and cerebral arteries suggests a potential for cerebrovascular and myocardial ischemia. Theoretically, the intracranial steal phenomenon, in which redistribution of blood flow away from the hemisphere ipsilateral to the highly stenotic artery, could lead to transient cerebral ischemia or cerebral infarction. In a large study using dipyridamole as a stress agent to thallium myocardial perfusion images, serious adverse events were few (*10*). The complication of a transient ischemic attack or cerebral, ischemic infarction after intravenous dipyridamole is rare (*14,15*). Precautions for the procedure are mandatory. We monitored blood pressure and EKG during and for 20 min after intravenous infusion of dipyridamole. Also, parenteral aminophylline (75–100 mg) was available. In patients with a history of unstable angina, acute myocardial infarction and bronchial asthma, use of intravenous dipyridamole stress should be avoided (*10*). Because of the prominent effect of hypoperfusion demonstrated in this case study, the dipyridamole SPECT study should not be performed during acute cerebral ischemia.

ACKNOWLEDGEMENTS

We thank Carol G. Crain for administrative support and Gerald W. Stone and Eilene B. Harp for their technical assistance during SPECT scanning.

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