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# Brain SPECT and the Effect of Cerebral Angioplasty in Delayed Ischemia due to Vasospasm

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Cerebral vasospasm is a major determinant of outcome after subarachnoid hemorrhage (SAH). Brain SPECT with  $^{99m}\text{Tc}$ -HMPAO was obtained before and after cerebral angioplasty in 10 patients with delayed ischemia due to vasospasm. Eight patients had clinically evident neurologic improvement after the procedure. Visual interpretation and an internal-reference (cerebellum), manual, semi-quantitative region of interest (ROI) analysis revealed improvement of regional cerebral blood flow (rCBF) in 9 out of 10. There were disagreements between the visual and ROI analysis in the two that did not improve clinically. For all 10, the average increase per anterior circulation vessel dilated ( $n = 17$ ) was 8.8% by comparison of the corticocerebellar ratios. For the eight that improved, the average increase was 10.5%. Brain SPECT is valuable for evaluating delayed cerebral ischemia caused by vasospasm after SAH and is useful to document the changes in rCBF induced by angioplasty. It is possible that SPECT may be useful to detect critical reductions in perfusion before clinical deficits develop, thereby offering the potential to identify candidates for early treatment with angioplasty.

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Cerebral vasospasm is one of the major complications causing death and disability after subarachnoid hemorrhage (SAH) (1). Previous work by the authors and from other institutions has shown the value of the noninvasive assessment of regional cerebral blood flow (rCBF) by single-photon emission computed tomography (SPECT) during vasospasm, which occurs in up to 75% of patients with SAH (2-4). The cerebral ischemia that is manifested as new neurologic deficits occurs in about 30% of SAH patients and is described as "delayed" because it usually occurs not on presentation, but during a period of 4 to 12 days after the hemorrhage. However, if a patient had a

sentinel bleed prior to the presenting SAH, vasospasm might be present on admission. In many patients it is not possible to know if such sentinel bleeds have occurred.

Standard treatment of vasospasm has included hypervolemic hemodilution, hyperdynamic hypertension and calcium channel antagonists (5-8). More recently, percutaneous transluminal angioplasty has shown effectiveness in treating patients with ischemic neurologic deficits due to vasospasm, which have been refractory to other therapies (9-12). First introduced by Zubkov et al. in 1984, this technique uses a microballoon catheter which is inserted in the narrowed arteries of the brain and then is used to mechanically dilate them (10). The procedure is primarily performed on the branch vessels of the Circle of Willis (Fig. 1). These vessels include the internal carotid, proximal segments of the middle cerebral, anterior cerebral and rarely, posterior cerebral arteries. Also, the posterior circulation may be dilated directly via the vertebro-basilar approach. The restoration of blood flow to the ischemic areas has resulted in improved neurologic function (11). Persistent dilation of the arteries has been demonstrated by transcranial Doppler (TCD) (12). The aim of this study was to demonstrate the effect of angioplasty on regional cerebral blood flow (rCBF) with  $^{99m}\text{Tc}$ -HMPAO SPECT (13) and to quantify the change.

## MATERIALS AND METHODS

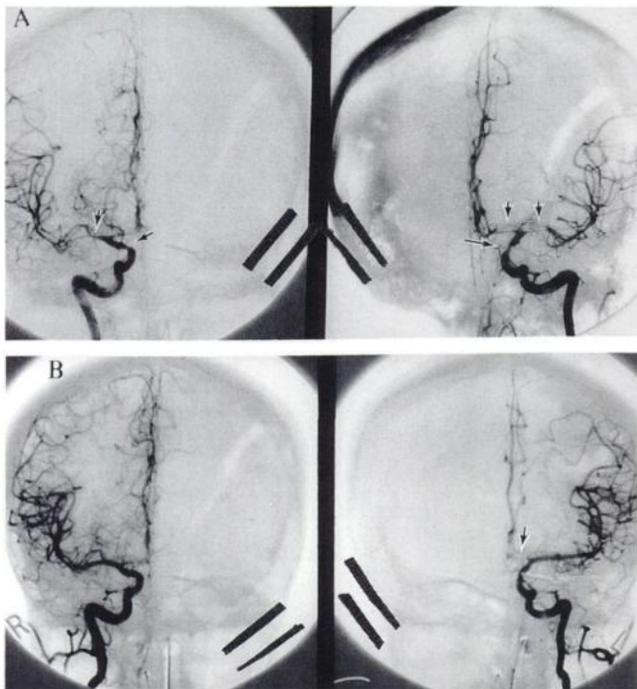
### Subjects

Between February 23, 1989 and October 3, 1991, ten patients had SPECT brain studies before and after cerebral angioplasty (Table 1). Nine patients had aneurysmal subarachnoid hemorrhage and one patient (#4) had post-traumatic SAH. For the nine patients with aneurysms, clipping was performed before angioplasty. For the angioplasty procedure, informed consent was obtained from the patient or patient representative. One patient (#1) had the pre-angioplasty SPECT within 48 hr prior to the procedure and repeat SPECT within 12 hr after the angioplasty. All others had the SPECT studies within 12 hr before and after the procedure. The pre-angioplasty SPECT scan was done in a range from 2 to 12 days after admission.

Four patients had prior brain SPECT within 3 days of the pre-

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**FIGURE 1.** (A) Pre-angioplasty angiogram of Patient 2 (see Table 1) from bilateral internal carotid artery injections (left on right side of photo, right on left). Arrows show right middle cerebral, right supraclinoid carotid, left middle cerebral, left anterior cerebral and left supraclinoid carotid arterial spasm. (B) Post-angioplasty angiogram. Residual stenosis is present in the left ACA (arrow) which was not amenable to balloon dilatation because it could not be reached. Because of the successful dilatation of the other vessels and restoration of good collateral circulation, however, the patient did not sustain an infarct. This patient had no residual regional cerebral blood flow deficit on the post-angioplasty SPECT.

angioplasty SPECT. These four patients were asymptomatic from vasospasm at the time of the "pre-pre-angioplasty" SPECT but had evidence of vasospasm on TCD exams. Therefore, a total of 24 brain SPECT studies from 10 patients were analyzed.

### Imaging Procedures: Processing

Delayed tomography was obtained with a GE 400AT camera (GE Medical Systems, Milwaukee, WI) linked to a Microdelta Computer (Siemens Medical Systems, Hoffman Estates, IL) after intravenous administration of 30 mCi (1110 MBq)  $^{99m}\text{Tc}$ -hexamethyl propyleneamine oxime (HMPAO, Ceretec, Medi-Physics, Amersham, Arlington Heights, IL). The delay before imaging was variable from 15 min postinjection to usually 45 min or longer after injection, but the timing of initiation of imaging after injection was approximately the same for the pre- and post-angioplasty tomograms of each individual patient. An energy window of 20% was centered on the  $^{99m}\text{Tc}$  peak for all studies. Tomography was performed with either a LEAP collimator at 20 sec/stop or a low-energy, high-resolution collimator at 25 sec/stop over 64 angles. Each patient had the same collimator used for both the pre- and post-angioplasty SPECT. Patients were positioned manually with the canthomeatal line perpendicular to the plane of the camera face. Transverse images were reconstructed with flood and center of rotation corrections, Butterworth filtered backprojection and attenuation correction. Recon-

structed single-pixel (6.25 mm) slices began with the most inferior portion of the cerebellum and terminated with the vertex. Images were group added to become 12.5 mm thick slices.

SPECT images were initially interpreted visually in the three standard axes, without region of interest (ROI) analysis (Fig. 2). Visual image interpretation was comprised by subjectively describing locations of reduced uptake relative to the cerebellum and/or contralateral brain in size (large, moderate, small) and severity (severe, moderate, mild).

### ROI Generation and Analysis

Based on knowledge of the dilated anterior circulation vessel, manually drawn ROIs approximating the involved arterial bed (14) were applied on the pre-angioplasty transverse images. Mirror regions were applied if, for example, both middle cerebral arteries were dilated. Regions for each individual patient were duplicated from the pre-angioplasty study and placed on the same location of vascular territory on the same co-registered slices of the post-angioplasty transverse images. In addition, an ROI based on a threshold of 66% (red-yellow interface) of the pixel with the most activity (white) in the whole brain was drawn around the cerebellar slice that had the most activity and demonstrated the hemispheres well, for both the pre- and postangioplasty exams. If crossed cerebellar diaschisis was present, only the cerebellar hemisphere with the most activity was used. Two to four 2-pixel thick slices based on visual extent of abnormality were analyzed for both the pre and the post-angioplasty SPECT studies (Fig. 3).

Corticocerebellar ratios were generated by dividing the average count per pixel in the region of the cortex by the average count per pixel in the cerebellar region of reference. Corticocerebellar (CCR) ratios for each 2-pixel thick slice (2 to 4 per vascular territory) were averaged to generate an average ratio for CCR per vascular territory before and after angioplasty. The patients with known vertebro-basilar artery spasm by angiography (whether having undergone dilation of the vertebro-basilar arteries or not) were noted, but no correction or compensation for alteration of the reference region could be logically made. The difference between the ratios pre- and post-angioplasty was obtained by subtraction and the difference expressed as a percentage based on a ratio of 1.0 (anterior circulation cortical average counts per pixel divided by cerebellar reference region average counts per pixel) as 100%.

In addition, the average CCR for the SPECT studies on four asymptomatic patients within three days prior to the pre-angioplasty SPECT were calculated with ROIs applied based on visual assessment of the area of greatest perfusion reduction.

### Statistics

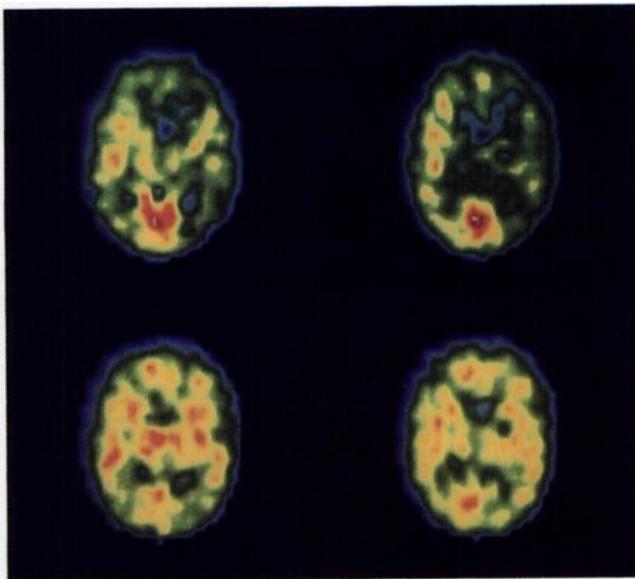
Corticocerebellar ratios were expressed with  $\pm$  standard error of the mean (s.e.m.) based on variance calculated from counts in the regions. Statistical comparison of the ratios before and after angioplasty was achieved by using the Wilcoxon matched pairs sign test in each of 17 anterior circulation vessels dilated. The level of statistical significance was selected at  $p < 0.01$ . Individual territory corticocerebellar ratios  $\pm$  s.e.m., and mean ratios  $\pm$  standard deviation (s.d.) pre- and post-angioplasty for all patients are shown in Table 2. The mean ratio  $\pm$  s.d. for the "pre-pre-angioplasty" SPECT for four asymptomatic patients is shown in Table 3.

### Angiograms and Head CT Scans

Angiograms were performed on all patients before and after angioplasty. Vasospasm was described as visually evident narrow-

**TABLE 1**  
Patient Data

Patient no.	Age	SPECT visual assessment		Crossed cerebellar diaschisis	Infarct on follow-up CT		Vertebro-Basilar arterial spasm		Neurologic function	
		Improved	Not improved		Yes	No	Yes	No	Improved	Not improved
1	63		x	No	Left frontal				x	x
2	46	x (No residual deficit)		Yes		x	x (Dilated)		x	
3	45	x (Residual deficit)		Yes	Right hemisphere			x	x	
4	19	x (Residual deficit)		Yes	Left frontal		x (Dilated)		x	
5	48	x (Residual deficit)		NA	Right temporal			x	x	
6	40	x (Residual deficit)		Yes	Left temporal			x	x	
7	40	x (Residual deficit)		No	Bilateral MCA infarcts		x (Not dilated)			
8	58	x (No residual deficit)		No		x	x (Not dilated)		x	
9	55	x (Residual deficit)		Yes	Bifrontal infarcts and midbrain infarct			x	x	
10	49	x (Residual deficit)		No	Right frontal, right occipital			x	x	
<b>Total</b>		<b>9</b>	<b>1</b>	<b>5</b>		<b>8</b>	<b>2</b>	<b>4</b>	<b>6</b>	<b>8</b>



**FIGURE 2.** SPECT transverse images before (top) and after (bottom) angioplasty in Patient 4 (see Table 1). There are large areas of severely reduced uptake in the MCA distributions bilaterally on the pre-angioplasty images. Improved rCBF is visually appreciated on the post-angioplasty images with the most remarkable improvement in the left middle cerebral artery distribution. This patient had a residual rCBF deficit in the left frontal region and sustained a small infarct in that location.

ing in the cerebral arteries. All patients had noncontrast head CT scans before (usually within hours) and within 3–7 days after the angioplasty (Table 1). The delay of 3–7 days was used to allow time for infarction to be evident if it was present. CT scans were read as: normal with operative site changes; abnormal with edema, hemorrhage; abnormal with ischemic changes: loss of gray-white differentiation, hypodensity; or abnormal with definite infarction. Small infarcts were comprised by zones substantially less than a vascular territory and also less than 2 cm in diameter. Large infarcts usually comprised whole vascular territories and measured at least 2.5 cm or more in diameter.

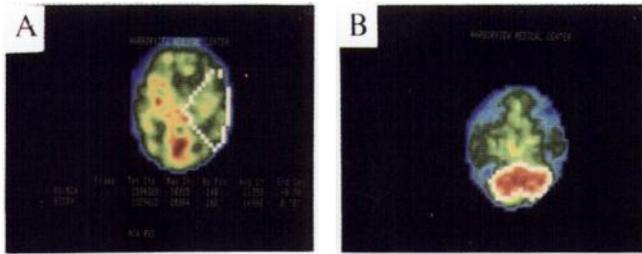
### Neurologic Exams

Neurologic status was recorded by members of the neurological surgery staff. Improved status after angioplasty was noted in the medical record. Improvement was characterized by increase in the Glasgow Coma Scale of at least two points, increased level of consciousness and responsiveness, and improved motor strength or loss of pronator drift (when it was present prior to angioplasty). No improvement in status was also noted in the medical record. No quantitative scale for gauging the degree of neurologic recovery was used.

## RESULTS

### Clinical Outcome

Eight patients had neurologic improvement resulting from the cerebral angioplasty (Table 1). The neurological



**FIGURE 3.** ROI generation for Patient 4 in Figure 2. (A) Left middle cerebral artery ROI (in white, marker line) with statistics. (B) Cerebellar ROI (in white, marker line at red-yellow interface). Semiquantitative analysis revealed an improvement in left middle cerebral territorial blood flow of 20% by corticocerebellar ratio comparison of the pre- and post-angioplasty values.

surgery staff noted the improvement or lack of improvement (see Materials and Methods section) in the patient's medical record. Two patients did not improve.

### Perfusion Changes in Patients with Neurologic Improvement

Visual interpretation revealed improvement of perfusion in all eight patients who had clinical improvement. Quantitative analysis of corticocerebellar ratio differences after and before angioplasty showed a mean increase in rCBF of 10.5% in these eight patients.

The status of residual perfusion deficits correlated strongly with final CT evidence of injury (Table 1). The two patients who had no residual perfusion deficit on the post-angioplasty SPECT did not have infarction on subsequent CT at 3 to 7 days. One of these patients (#8) had ischemic changes in the left frontal lobe on the pre-angioplasty CT scan which appeared to have resolved entirely on the post-angioplasty follow-up CT. The other six who had clinical and rCBF improvement but also had visually

evident residual SPECT deficit after angioplasty had evidence of cortical injury on later CT scans (infarct, encephalomalacia, focal volume loss). Five of these six patients had had evidence of infarction, parenchymal hemorrhage or ischemic changes on their pre-angioplasty CT scans. The other patient that developed infarction had a delayed stroke 4 days after the angioplasty but had not had ischemic changes on the pre-angioplasty CT.

Of the six that improved but sustained neuronal damage on CT, there were two who had large infarcts (>2.5 cm). The visual assessment of the residual deficit on SPECT was that these two patients had more extensive and severe reduction in rCBF as compared to the other four. The other four patients had small zones of cortical injury (<2 cm).

### Perfusion Changes in Patients Without Neurologic Improvement

There were two patients (#1 and #7) who did not improve clinically after angioplasty despite the angiograph-

**TABLE 2**  
Pre- and Post-Semiquantitative Results

Patient no.	Vessel(s)	Corticocerebellar ratio (%)	
		Pre	Post
1	LACA	65.2 ± 0.8 (s.e.m.)	71.7 ± 0.9 (s.e.m.)
	LMCA	73.2 ± 0.9	86.9 ± 1.0
	LMCA	80.2 ± 1.3	96.0 ± 0.8
2*	RMCA	83.8 ± 1.3	90.7 ± 0.8
3	RMCA	61.3 ± 0.8	86.9 ± 1.4
	LMCA	74.9 ± 0.7	94.9 ± 0.8
4*	RMCA	82.5 ± 0.7	90.9 ± 0.8
5	RMCA	68.1 ± 0.9	69.8 ± 0.8
6	LMCA	69.3 ± 0.9	80.7 ± 1.1
	LMCA	87.0 ± 1.3	80.6 ± 1.1
7*	RMCA	77.8 ± 1.1	67.3 ± 0.9
	LMCA	88.9 ± 1.1	93.8 ± 1.2
8*	RMCA	87.6 ± 1.1	84.6 ± 1.1
	LMCA	99.0 ± 1.1	115.0 ± 1.1
9	RMCA	94.3 ± 1.1	110.8 ± 1.1
	LMCA	93.0 ± 0.9	105.5 ± 1.3
10	RMCA	87.1 ± 0.8	97.6 ± 1.2
Summary	10 Patients	Average	
	17 Vessels	80.8 ± 10.9 (s.d.)	89.6 ± 13.5 (s.d.)
	14 Improved		
	3 Not improved		
		Difference	+8.8%

\* Vertebro-basilar artery spasm.

**TABLE 3**  
Semiquantitative Results of SPECT Prior to Pre-angioplasty in Four Asymptomatic Patients

Patient no.	Days prior to pre-angioplasty SPECT		Corticocerebellar ratio (%)
2	3	LMCA	85.3 ± 1.0 (s.e.m.)
		RMCA	84.5 ± 1.0
3	1	RMCA	86.8 ± 0.9
5	2	RMCA	65.1 ± 1.1
8	1	LMCA	78.5 ± 1.0
Total 4 patients		Average	80.0 ± 8.9 (s.d.)

ically evident primary success in dilation of the narrowed vessels. Both had large infarcts (>2.5 cm) comprising substantial portions of vascular territories on the pre-angioplasty CT scans. Patient 1 had ischemia for 2 days before the balloon dilatation, as the pre-angioplasty SPECT exam that showed the reduced perfusion preceded the angioplasty procedure by 48 hr. Patient 7 already had evidence of bilateral MCA infarcts on CT prior to the angioplasty. On quantitative analysis, the mean change in the corticocerebellar ratios for both was +0.8% (n = 4 vessels dilated). This number most likely represents a statistically negligible change even though this was a small group.

There was disagreement of visual interpretation and semiquantitative analysis in the two patients who did not improve. Patient 1 had minimal improvement in the left frontal cortex (anterior cerebral artery territory) on quantitation with no improvement noted in this territory visually. There was more significant improvement in the left middle cerebral artery territory on quantitation which was not initially appreciated visually, but was seen in retrospect. Although this patient sustained a large left anterior cerebral artery infarction and appeared not to improve clinically, no infarct was present in the left middle cerebral artery territory on subsequent CT. Patient 7 had reduced perfusion on quantitative analysis of the ROIs of both vascular beds of the vessels dilated, but had improvement of blood flow in zones adjacent to the infarcts on visual interpretation. Visual interpretation, however, recorded that the large infarcts present on the pre-angioplasty SPECT (as indicated by CT findings and interpreted as infarcts on the pre-SPECT due to "severe" regional reduction of tracer uptake in the MCA distributions as noted by visual inspection) had not changed in size or degree of uptake. Decreasing uptake over the time of the two studies within the central zones or gray-white core of the bilateral middle cerebral infarcts contained within the ROIs may have caused this discrepancy. Also, this patient had a variable of vasospasm within the basilar artery which could have caused changes in uptake in the cerebellar region of reference between the two studies.

#### Crossed Cerebellar Diaschisis

Evidence of crossed cerebellar diaschisis (CCD) was assessed on the pre-angioplasty SPECT studies (Table 1).

One patient (#5) had a cerebellar hemorrhage and could not be included in the evaluation of CCD. Five of nine patients demonstrated CCD on the pre-angioplasty SPECT. There appears to be no relationship between its absence or presence before angioplasty and the subsequent lack or development of infarction. For example, one of the patients with no residual deficit on SPECT and no infarct on CT had CCD on the pre-angioplasty SPECT. Four of the patients who had infarcts did not demonstrate CCD on the pre-angioplasty study. The presence of CCD, however, directed the generation of the cerebellar ROI for quantitative analysis.

#### Vertebro-basilar Vasospasm

Four patients had vertebro-basilar arterial spasm, two of whom had vertebro-basilar angioplasty. These patients were duly noted (Table 1), as changes in the reference cerebellar region used for normalization could not be compensated for nor controlled. Nevertheless, the significance of these patients' results led us to include them in the semi-quantitative analysis.

#### Corticocerebellar Ratios for Symptomatic and Asymptomatic Patients

The mean value for vascular territorial uptake per vessel dilated on the pre-angioplasty SPECT was 80.8% ± 10.8% (s.d.). The mean post-angioplasty ratio was 89.6% ± 13.5% (s.d.). Semiquantitative ROI analysis of the pre- and post-angioplasty SPECT revealed an overall average improvement for each anterior (i.e., carotid) circulation vessel dilated (n = 17) of 8.8% for the CCR method (Table 2) in patients with symptoms who underwent angioplasty. The differences between the ratios pre- and post-angioplasty reached statistical significance (p < 0.002) on the Wilcoxon matched pairs sign test. The large standard deviations of the means most likely are representative of small sample sizes and variability in degrees of ischemia among patients which are not quantifiable in absolute numbers by this method. However, the direction of rCBF change was significant by the statistical method chosen.

In the four asymptomatic patients who had prior brain SPECT within 3 days before the pre-angioplasty study the mean corticocerebellar ratio was 80.0% ± 8.9% (s.d.) (Table 3).

#### DISCUSSION

In this study, the effects of percutaneous transluminal cerebral angioplasty on regional cerebral blood flow and neurologic function was evaluated by brain SPECT and neurologic exam in 10 patients. The results indicate a beneficial effect of angioplasty in terms of neurologic improvement as well as visual and quantitative evidence of restoration of blood flow to ischemic regions. However, despite the success of this treatment, it is disturbing to note that infarctions occurred in many of the patients. There were eight patients who had evidence of zones of infarct, ischemia or focal hemorrhage on CT prior to

angioplasty, and therefore, angioplasty could not have reduced or reversed the infarctions that were already present. However, the question remains: when is the appropriate time to intervene in patients with vasospasm and are we now acting too late to prevent many of the infarcts?

It is estimated that 80% of patients with cerebral vasospasm which is angiographically graded as "severe" will develop a clinical deficit corresponding to ischemia in the bed of the narrowed vessel. The overall incidence of clinical vasospasm, also known as delayed cerebral ischemia, after subarachnoid hemorrhage is approximately 30% (1). There is a "subset," or better stated, a "stage" of cerebral vasospasm which could bear the title "subclinical vasospasm" (2). Patients with cerebral vasospasm are usually treated with the conventional therapies. At our institution, cerebral angioplasty is employed when these therapies are failing and the patient begins to demonstrate signs of neurologic deterioration, or "clinical vasospasm," despite optimal hemodynamic and medical treatment. Could non-invasive tests, such as SPECT combined with transcranial Doppler ultrasound, identify the patients in the precursor stage or subset of subclinical vasospasm who most likely will later develop observable clinical deficits? Given the extremely low incidence of adverse effects due to angioplasty in our institution, perhaps early intervention is not unreasonable (9).

Cerebrovascular autoregulation and collateral flow may maintain rCBF in the face of "severe" angiographic spasm. Alteration of autoregulation is known to occur after subarachnoid hemorrhage (15). SPECT corticocerebellar ratios combined with changes in TCD measured velocities may identify patients in whom these homeostatic mechanisms are failing and will soon develop ischemic deficits. At the other end of the spectrum, we have shown that SPECT may be normal and patients remain asymptomatic at the same time that TCD velocities are very elevated in single vessels, due to preserved autoregulation and collateral flow (2). Therefore, TCD velocities by themselves are not reflective of regional cerebral blood flow when autoregulation is intact and especially during conditions of rapidly changing blood flows and blood pressures (16). For example, we have previously reported, by a direct comparison of TCD and SPECT, that despite primary success of angioplasty in persistent dilation of a narrowed artery, which TCD recorded and angiography corroborated, SPECT has revealed, fortunately rarely, no improvement in rCBF that correlated with tissue death (17). We therefore find that SPECT and TCD are useful and complementary in patients with vasospasm who are undergoing hemodynamic treatment as these tests evaluate rCBF and the degree of vessel narrowing, respectively, ie., function and structure (2).

Of great concern is that by the time the patient develops clinically observable deficits, cerebral infarction may already be in progress. How might we identify patients at risk for developing neurologic deficits from cerebral vaso-

spasm? The results in four patients who had SPECT obtained within 3 days of the pre-angioplasty study showed an average ratio of 80.0% by the corticocerebellar ratio method. Since these patients later developed ischemic neurologic deficits, these values obtained during the antecedent, asymptomatic period may be important. Perhaps these values might serve as "thresholds" for considering cerebral angioplasty in the "subclinical vasospasm" patient who is on the brink of symptomatic ischemia and possible infarction.

There are drawbacks to SPECT semi-quantitative analysis. The term "semiquantitative" indicates that absolute blood flow values are not given by this method. Nevertheless, there have been attempts to characterize cerebral disease states with the employment of similar internal-reference quantitative analyses. To compare our results of an internal-reference ROI analysis of patients with ischemia, it is worthwhile to explore what others have found with cerebral blood flow radiopharmaceuticals in similar situations. Nakano et al. described infarcted and symptomatic blood flow thresholds for [<sup>123</sup>I]iodoamphetamine (IMP) with lesion-to-normal ratios of 39%–48% and 65%–72%, respectively (18). This same group also described the lesion-to-normal ratios for <sup>99m</sup>Tc-HMPAO as significantly higher than those for [<sup>123</sup>I]IMP in cerebrovascular disease patients reflecting substantial differences between these two radiopharmaceuticals (19). The ratios that were obtained in our aforementioned 4 "subclinical" patients are in keeping with the latter report of <sup>99m</sup>Tc-HMPAO, but of course, they represent corticocerebellar ratios, not lesion-to-contralateral-normal ratios. The above studies inferred that the contralateral brain was normal for standardization purposes. The same cannot be assumed for patients with cerebral vasospasm. However, we speculate that a CCR method is the most appropriate internal-reference ROI analytic scheme for patients with vasospasm because the cerebellum is more richly supplied with collateral circulation than is the neo-cortex.

In this study, we chose to use normalization to the cerebellum for quantitation as has been done by other authors investigating an array of cerebral and neuro-psychiatric diseases (20–22). Yet, as evident in our patients, the reference region of the cerebellum might also be affected by vasospasm, and there is no logical compensation for this semi-quantitative method when practically all the vessels of the brain might be involved. Furthermore, corticocerebellar ratios do not reflect global changes in blood flow caused by angioplasty if all vessels are equally affected. As noted in the article by Gemmell et al. (21), it is not possible to generate absolute units of rCBF by conventional SPECT with <sup>99m</sup>Tc-HMPAO (i.e., no arterial sampling) without the ascertainment of a reference region rCBF by a truly quantitative method such as <sup>133</sup>Xe washout or PET blood flow studies. Also, Lassen correction (23) of HMPAO data, which attempts to account for incomplete retention of tracer at high flow regions, can bring rCBF

SPECT into linear agreement with PET rCBF values (21). But, Gemmell et al. showed that this manipulation of the data is only valid when the Lassen correction algorithm uses an absolute value of rCBF generated by PET from the reference high flow region, usually the cerebellum, in the equation.

Other issues for accurate quantitation concern our use of radioactivity and tomography. Scatter correction was not attempted in this study, but given that the same energy windows and collimators were used in each patient for SPECT before and after angioplasty, the effect of scatter should have been uniform for each individual patient. For a truly quantitative study, scatter correction would necessarily be part of the image processing. Attenuation correction was done in this study using a first order Chang boundary method (24). Yet, this technique, if employed improperly and not critically evaluated, could enter significant systematic errors in the data, particularly for side-to-side ratios. Transmission tomography and subsequent map correction of attenuation, as done in quantitative PET, would be a more exacting approach.

Another significant problem for our particular study was the need for a visually directed, manual depiction of the ROIs, which entails possible and, to some degree, probable operator error. As yet there is no commercially available processing software that will semiautomatically overlay estimated vascular distributions on the transverse slices and also outline the cerebellar reference region. A semi-automatic template program would reduce the operator influence on variation of the regions. Despite these limitations, meticulous production and placement of the regions for both the pre- and the post-angioplasty studies was possible (25). Serial studies in the same patients with obvious blood flow abnormalities in fairly large territories made the operator (DHL) confident in the generation of the vascular distribution ROIs.

We have not tested the inter- and intra-observer variability of this manual ROI generation at our institution. Because it is a purely manual technique, we estimate that its variability from both frames of reference would be unacceptably high. Furthermore, it would be of value to know the CCR values in age-matched controls. We have not generated a normal file but have future projects in which the semi-automatic analysis of normal peoples' values will be essential to use in comparison to pathologic states (particularly for less obvious rCBF abnormalities as may be present in psychiatric or early dementing diseases). A normal database for <sup>99m</sup>Tc-HMPAO regional uptakes based on vascular distributions would be very useful for semi-quantitative analysis of SPECT in the specific subset of cerebrovascular disease patients as well. The most anatomically exacting study of regional uptakes of <sup>99m</sup>Tc-HMPAO in normal people has been reported by Waldemar et al. (26) but this work did not derive regions based on vascular beds nor did the authors assess the intra- and inter-observer variability of their semi-automatic, cortico-

cerebellar ratio method. However, with this scheme as a model, we plan to abandon the manual ROI analysis method once we have a workable semi-automatic program that could be tested for intra- and inter-observer variability.

In summary, despite the limitations of the semi-quantitative method and possible variation of the reference region, we have shown that SPECT of regional cerebral perfusion with <sup>99m</sup>Tc-HMPAO depicts changes in blood flow due to cerebral angioplasty in patients with delayed cerebral ischemia after subarachnoid hemorrhage. The clinical improvement caused by the angioplasty correlated well with the SPECT findings. Given the complicated nature of these patients and the other neurologic insults that they had suffered as evidenced by pre-existing damaged zones on the pre-angioplasty CT, it is still quite clear that cerebral angioplasty significantly improved the outcome in 8 out of the 10 patients. Visual and semiquantitative analysis of the images are both valuable, although there were conflicting results in the two patients who did not improve. The issue for further investigation is whether noninvasive tests such as combined TCD and brain SPECT with semi-automatic ROI analysis will be able to predict which "subclinical" vasospasm patients merit consideration for early use of angioplasty to prevent infarcts that occur in this devastating disease.

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