A Single-Photon Emission Computed Tomography Study of Hypoperfusion After Subarachnoid Hemorrhage

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We used single-photon emission computed tomography with technetium-99m hexamethylpropylenamine oxime in 18 studies on 13 patients with subarachnoid hemorrhage to determine whether any changes in cerebral blood flow could be correlated with clinical or computed tomographic evidence of delayed ischemia. Among the seven patients without focal neurologic deficits, regional cerebral hypoperfusion was demonstrated in only one who died. Among the 10 patients with aneurysmal subarachnoid hemorrhage, one died before surgery, and six developed postoperative delayed ischemic deficits, of whom two died. Among the patients with angiographically documented aneurysms, regional hypoperfusion correlated with the presence and severity of delayed neurologic deficits, whereas correlative computed tomographic scans showed either early infarction or no relevant abnormality. This technique facilitates early diagnosis of cerebral tissue hypoperfusion due to vasospasm after subarachnoid hemorrhage. (Stroke 1990;21:252-259)

Cerebral vasospasm causing delayed ischemic neurologic deficits complicates subarachnoid hemorrhage (SAH) in approximately 30% of patients.1 Symptomatic cerebral vasospasm typically occurs >72 hours after an SAH and peaks approximately 6–10 days after an SAH, constituting a prime cause of morbidity and mortality in patients with this condition.2

In addition to vasospasm, other causes of delayed neurologic deterioration after SAH include recurrent hemorrhage, elevated intracranial pressure, the development of hydrocephalus, and electrolyte disorders, particularly hyponatremia.1,2 While urgent computed tomography (CT) is usually performed to detect recurrent hemorrhage or hydrocephalus,1 the development of low-attenuation areas on CT represents a late finding in patients with frank infarction due to vasospasm.

Definitive diagnosis of cerebral vasospasm has previously depended on the angiographic demonstration of reduced vascular luminal diameter, but angiography is invasive and potentially hazardous and carries the risk of exacerbation of vasospasm.3,4 With the introduction of specific therapies for cerebral vasospasm, including the use of nimodipine5 and the institution of hypervolemic hypertension,1-2 the early identification of tissue hypoperfusion by a noninvasive imaging technique would be of diagnostic value and could provide an objective basis for the evaluation of therapy. Transcranial Doppler ultrasonography, providing data on cerebral arterial erythrocyte velocities, has been shown to be useful in both predicting and diagnosing arterial vasospasm6-9 but does not provide direct information concerning cerebral tissue perfusion.10

Single-photon emission computed tomography (SPECT) using technetium-99m (Tc-99m) hexamethylene propylenamine oxime (HM-PAO) provides tomographic images of cerebral perfusion.11-14 This chelated compound is lipophilic, readily crosses the blood–brain barrier, and has a high first-pass cerebral extraction with long-term retention. Using the intravenous Tc-99m HM-PAO SPECT technique, cerebral blood flow (CBF) maps are obtained that are...
TABLE 1. Cerebral Blood Flow in Seven Patients With Progressive Neurologic Deficits

<table>
<thead>
<tr>
<th>Patient</th>
<th>Computed tomography</th>
<th>Single-photon emission computed tomography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative death</td>
<td>Focal blood</td>
<td>Focal reduction</td>
</tr>
<tr>
<td>1</td>
<td>Postoperative delayed ischemic deficits</td>
<td>Focal reduction &gt; extent of changes on computed tomography (died 2 days after surgery)</td>
</tr>
<tr>
<td>2</td>
<td>Low-attenuation areas</td>
<td>Focal reduction &gt; extent of changes on computed tomography (died 4 days after surgery)</td>
</tr>
<tr>
<td>3</td>
<td>Low-attenuation areas</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>Focal reduction</td>
</tr>
<tr>
<td>5</td>
<td>Low-attenuation areas</td>
<td>Focal reduction</td>
</tr>
<tr>
<td>6</td>
<td>Low-attenuation areas</td>
<td>Focal reduction &gt; extent of changes on computed tomography</td>
</tr>
<tr>
<td>7</td>
<td>Low-attenuation areas</td>
<td>Focal reduction &gt; extent of changes on computed tomography</td>
</tr>
</tbody>
</table>

 comparable with those derived using other tomographic methods, such as SPECT with iodine-123-labeled amines.13 There have been few reported studies using tomographic CBF techniques in patients with SAH,10–12 and only one other study13 using Tc-99m HM-PAO.

Using SPECT with Tc-99m HM-PAO, we aimed to determine whether changes in cerebral tissue perfusion in patients with SAH predicted or were correlated with the onset of delayed ischemic deficits, whether the technique provided data additional to that provided by CT at the time of clinical deterioration, and whether the technique provided prognostic data concerning patient outcome.

Subjects and Methods

We studied 13 nonconsecutive patients with SAH at the Royal Melbourne Hospital. There were 2 men and 11 women, and their mean age was 47 years. All 13 patients had at least one CT scan, and all had four-vessel angiography following the diagnosis of SAH. Angiography documented aneurysmal SAH in

FIGURE 1. Computed tomogram (left) and cerebral angiogram (right) of patient with subarachnoid hemorrhage due to ruptured right middle cerebral artery aneurysm (arrow). Note interhemispheric blood and focal collection in right sylvian region at site of aneurysm rupture.
Hypoperfusion in SAH

FIGURE 2. Computed tomograms (left) and single-photon emission computed tomograms (right) following delayed ischemic deficit in patient with subarachnoid hemorrhage due to ruptured right middle cerebral artery aneurysm shown in Figure 1. Note low-attenuation areas in addition to older hemorrhage in upper left but more extensive and severe depression of cerebral blood flow in both middle and anterior cerebral artery territories.

10, but in three patients with proven SAH angiography failed to show a causative lesion.

Surgery with clipping of the relevant aneurysm was performed in nine of the 10 patients with aneurysmal SAH; the other patient died before surgery could be performed. The three patients with normal angiograms and three of the nine surviving patients with aneurysmal SAH had uncomplicated clinical courses. The other six patients with aneurysmal SAH had delayed postoperative neurologic deterioration.

Cerebral vasospasm was diagnosed in five of these six patients on clinical grounds (development of drowsiness and focal neurologic deficits) when urgent CT failed to show other causes such as recurrent hemorrhage or hydrocephalus. Angiography was not repeated in these five patients, of whom two died of severe infarction with resultant cerebral swelling and brainstem herniation. In the sixth patient, a repeat angiogram demonstrated vascular spasm in the arterial territory of the ruptured aneurysm. The surviving four patients with aneurysmal SAH made varying degrees of neurologic recovery following postoperative neurorehabilitation.

We performed 18 intravenous Tc-99m HM-PAO (Ceretec, Amersham, Little Chalfont, U.K.) SPECT studies on the 13 patients, shortly after the onset of delayed ischemic deficits in six of the 10 patients with aneurysmal SAH. We repeated the SPECT study in five patients (four with aneurysmal SAH and one with a normal angiogram).

The CBF study consisted of 2.0-second anterior dynamic views following an intravenous bolus injection of 500 MBq of Tc-99m HM-PAO. An average labeling efficiency of 90% was achieved. The acquisition of anterior, posterior, right, and left lateral static views was commenced 5 minutes after the injection. Following the CBF study, a SPECT acquisition was obtained.

The SPECT study consisted of 64 40-second views over a 360° elliptical orbit. A parallel-hole low-energy all-purpose collimator was used with a cut-away head that allowed its close passage around the patient's skull. An average count rate of approximately 1,000 counts/sec was obtained from the cerebral tissues anteriorly. The SPECT study was acquired with a GE400AC Starcam gamma camera (Milwaukee, Wisconsin).
Reconstruction consisted of prefiltering using a Butterworth filter, with a critical frequency of 0.35–0.40 cycles/cm and a power factor of 10.0. Nine-millimeter-thick transaxial, coronal, and sagittal slices were produced, and attenuation correction was applied. Reconstruction was performed along anatomic planes of the brain. The initial SPECT studies were performed a mean of 4 days after the onset of the SAH.

Among the nine patients with aneurysmal SAH treated surgically, SPECT studies were performed during the early postoperative period in four. A second SPECT study was performed in four of these nine patients; two had both preoperative and postoperative SPECT studies and the other two patients had two sequential postoperative SPECT studies. In the six patients who demonstrated delayed ischemic deficits considered to be due to cerebral vasospasm, SPECT studies were performed within 18 hours after the clinical deterioration.

The SPECT studies provided semiquantitative regional count data displayed on colored, tomographic maps. The maps were evaluated for any evidence of interhemispheric asymmetry in the anterior cerebral artery, middle cerebral artery (MCA), or posterior cerebral artery territories by visual inspection and by using homologous 16-pixel, square regions of interest. Each pixel was 3 mm on a side; thus, the regions of interest were 12×12 mm. We were not able to study normal control volunteer subjects. Using the Tc-99m HM-PAO technique in 11 normal subjects, Podreka et al14 studied regional tracer distribution and interhemispheric asymmetries in count rates for 15 homologous regions and found that the mean ±2 SD interhemispheric difference for each region did not exceed 12%. Using the Tc-99m HM-PAO method, Buell et al19 used an interhemispheric asymmetry threshold of 10% for their diseased-to-undiseased ratios. We regarded an interhemispheric difference of ≥12% for homologous regions to indicate abnormal asymmetry.

The CT scans and cerebral angiograms were evaluated by a neuroradiologist without knowledge of the SPECT data. The SPECT studies were evaluated by nuclear medicine physicians without knowledge of the results of the radiologic studies. The patients were examined neurologically on a daily basis, without knowledge of the CBF results.

Results

No focal clinical deficits at any stage were found in three patients with SAH of unknown cause and in three patients with aneurysmal SAH (one with a pericallosal artery aneurysm and two with anterior communicating artery aneurysms). Cerebral angiograms in these six patients showed no evidence of vasospasm. Subarachnoid blood was evident in most of these patients on the initial CT scan, and three patients had focal cerebral abnormalities. One patient had an incidental arachnoid cyst that was evident on both CT and SPECT scans, whereas another patient had an old lacunar infarct in the left thalamus and a normal SPECT scan; a small postoperative subdural hematoma was evident on both CT and SPECT scans in a third patient.

Progressive neurologic deficits were seen in the other seven patients (Table 1). Patient 1, who had a right MCA aneurysm, was drowsy on admission and had a mild left hemiplegia; CT scan showed evidence of focal blood in the right sylvian region. A correlative SPECT study showed reduced perfusion deep in the right hemisphere. This patient died without surgery.

The other six patients with progressive neurologic deficits all had early (<72 hours after onset) surgery for aneurysmal SAH and developed postoperative delayed ischemic deficits considered to be due to vasospasm. Two of these six (patients 2 and 3) died of massive cerebral infarction 2 and 4 days postoperatively, with depressed consciousness states and hemiplegia; neither patient had had evidence of vasospasm on the initial angiogram. Patient 2 had an SAH due to a ruptured right MCA aneurysm (Figure 1). A preoperative SPECT study when there were no focal central nervous system signs indicated a mild reduction in right MCA territory perfusion. Following clinical deterioration 2 days after surgery, a CT scan showed mild changes due to infarction in the right MCA territory, while the SPECT study showed severe CBF depression in both the entire MCA and anterior cerebral artery territories (Figure 2). The second patient who died (patient 3) developed left hemiplegia and drowsiness 4 days following surgery in which a right posterior communicating artery aneurysm had been clipped. Early changes of infarction in the superior division of the right MCA were shown on a CT scan (Figure 3), while a SPECT study showed a severe depression of CBF (60% interhemispheric asymmetry) in the superior division and an additional, milder depression (15% asymmetry) in the inferior division of the right MCA.

In the other four patients with delayed ischemic deficits of lesser severity, SPECT scans showed varying degrees of depression of cortical or deep perfusion that correlated anatomically with the neurologic deficit but were less severe than those seen in the two patients who died of severe infarction. Among these four patients, CT scans were either normal (in patients 4 and 5) or showed less extensive abnormalities than SPECT (in patients 6
and 7). Perfusion deficits were shown in arterial territories adjacent to the site of aneurysmal rupture. One patient had persistent dysphasia and cognitive problems indicating left cortical damage due to a delayed ischemic deficit following surgical clipping of a left internal carotid artery aneurysm. Whereas a CT scan showed only deep infarction adjacent to the left lateral ventricle, the SPECT studies showed both hypoperfusion correlating with this site and additional CBF depression in the left MCA-supplied cortex (14% interhemispheric asymmetry; Figure 4).

Discussion

These results indicate that regional hypoperfusion in patients with SAH can be demonstrated shortly after the onset of delayed ischemic neurologic deficits using SPECT with Tc-99m HM-PAO. The degree of regional hypoperfusion was correlated with the severity of the neurologic deficits. In the absence of neurologic abnormalities, the CBF studies were usually normal.

There have been a number of CBF studies in patients with SAH reported, the earlier investigations using nontomographic techniques. Using intravenous xenon-133, Merory et al. were unable to correlate the clinical stage of SAH with mean CBF values but found a postoperative association between CBF and consciousness state. Using the xenon-133 inhalation method, Geraud et al. found that higher CBF values predicted a favorable clinical outcome. Other investigators have correlated poor clinical grades after SAH with depression of CBF, although these nontomographic techniques were poorly correlated with angiographically demonstrated vasospasm and focal ischemia, probably due to poor spatial resolution. Utilizing the higher spatial resolution provided by the invasive intra-arterial xenon-133 technique, Voldby et al. correlated focal and global reductions of CBF with cerebral vasospasm. Hayashi et al. found that lower CBF was associated with higher resting intracranial pressure and with the development of hydrocephalus.

More recent studies have employed tomographic CBF techniques. Mickey et al. performed serial studies with SPECT and inhaled xenon-133 and found correlations between regional depression of CBF, delayed ischemic deficits, and arteriographic evidence of vasospasm; other patients with delayed ischemic deficits showed a global CBF reduction. Measuring both CBF and regional oxygen metabolism using positron emission tomography, Powers et al. distinguished reversibly ischemic from infarcted tissue in patients with hemiparesis due to vasospasm after aneurysmal SAH.

Rawluk et al. used SPECT with Tc-99m HM-PAO in seven patients with SAH and in six found focal CBF reduction related anatomically to the site of the ruptured aneurysm, although only two of these patients had evidence of correlative angiographic vasospasm. This technique has several advantages, which include the wide availability of the technetium gamma emitter, the ease of radiopharmaceutical preparation of the HM-PAO, the intravenous injection route, and image acquisition by a rotating gamma camera. While CBF cannot be quantified by this method, comparisons of count rates between hemispheres can provide a semiquantitative index of pathologic alterations in regional perfusion. However, bilateral or diffuse hypoperfusion may be undetected because absolute CBF values are not obtained.

The stable xenon-enhanced CT method has been used to map regional CBF in patients with acute cerebrovascular disease and can demonstrate hypoperfusion due to vasospasm after SAH. This technique also has some minor limitations, including mild cerebral side effects and the unknown effects of xenon on blood flow. Quantification of CBF in normal subjects and stroke patients using SPECT with N-isopropyl[123I]-iodoamphetamine has been recently reported.

Using transcranial Doppler ultrasonography, the finding of increased arterial erythrocyte velocity in patients with SAH and cerebral vasospasm has been an important recent advance. Increases in velocity, particularly when sudden, may precede the onset of delayed neurologic deficits by hours or days, but increased velocities have also been found in some patients with SAH and no neurologic deficits, consistent with reports of higher angiographic than clinical incidences of vasospasm in various studies. This discrepancy is understandable as the transcranial Doppler technique measures arterial erythrocyte velocity, which does not necessarily correlate with tissue perfusion (CBF). In the early stages of cerebral vasospasm, with lowered perfusion pressure, CBF may be unaffected due to the increased cerebral blood volume consequent upon autoregulation with vasodilatation of small blood vessels. There is likely to be a threshold for increased arterial erythrocyte velocity at which CBF begins to decline. In addition, there may be some patients with vasospasm in distal cerebral arteries not insonated by the transcranial Doppler technique in whom CBF might be reduced in spite of normal arterial erythrocyte velocities.

Only one study has compared cerebral arterial erythrocyte velocities measured by transcranial Doppler ultrasonography with CBF in patients with SAH. Sorker et al. found that CBF depression measured by stable xenon-enhanced CT and intravenous xenon-133 followed the elevation of arterial erythrocyte velocities and generally correlated with the clinical condition of the patients.

We conclude that brain SPECT with Tc-99m HM-PAO is a relatively accessible technique that can demonstrate varying degrees of regional tissue hypoperfusion in patients with delayed ischemic deficits following SAH. Additional studies of both cerebral arterial erythrocyte velocities and CBF are necessary to further elucidate the relation between arterial vasospasm and tissue perfusion in patients with SAH.
and to help define which subsets of patients might benefit from specific therapeutic modalities.

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References


KEY WORDS • cerebral blood flow • cerebral vasospasm • subarachnoid hemorrhage • tomography, x-ray computed
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