Predictive Value of Brain Perfusion
Single-Photon Emission Computed Tomography in Acute Ischemic Stroke

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We investigated 32 patients with completed ischemic stroke ≤6 hours after the onset of symptoms by means of computed tomography, cerebral angiography, and technetium-99m-labeled hexamethylpropyleneamine oxime single-photon emission computed tomography to study cerebral blood flow. Follow-up computed tomography and cerebral blood flow studies were performed 1 week and 1 month after admission. Poor outcome at 1 month was evident in 18 (78%) of the 23 patients with severe neurologic deficit on admission and in 11 (92%) of the 12 patients with severe hypoperfusion in the affected hemisphere on admission. All 10 patients with severe impairment of both neurologic status and cerebral blood flow had a poor outcome at 1 month. We detected severe hypoperfusion in patients with large lesions on computed tomograms or cerebral artery occlusions on angiograms. Cerebral blood flow had increased at the 1-week follow-up despite different clinical outcomes. Our data provide evidence that early evaluation of cerebral blood flow with single-photon emission computed tomography is useful to detect subgroups of patients with different clinical outcomes during the acute phase of ischemic stroke. (Stroke 1990;21:895-900)

Reliable and accurate predictions of final clinical outcome in patients with acute stroke are likely to be of value for both planning the care of individual patients and organizing therapeutic trials. The final amount of neuronal damage and degree of functional impairment depend on several factors, of which the duration of occlusion and the absolute decrease in regional cerebral blood flow during ischemia are of greatest importance.

Data are available on early CBF changes in experimental cerebral ischemia, but similar observations are lacking in humans. Changes during the first 24–48 hours after a stroke have been described using both positron emission tomography (PET) and single-photon emission computed tomography (SPECT). However, no data are available on CBF impairment in humans during the first 3–6 hours of an ischemic stroke or the correlation between CBF impairment and the presentation or clinical outcome of patients.

The aim of our study was to substantiate the clinical predictive value of early (within 6 hours) SPECT study of CBF and to evaluate the relations between morphologic and perfusion findings in patients with acute cerebral ischemia.

Subjects and Methods

We evaluated CBF using SPECT in 32 (19 men and 13 women, mean ± SD age 64.3 ± 14.7 years) of 80 patients with hemispheric ischemic stroke recruited ≤4 hours after the onset of symptoms. Ischemic stroke was diagnosed based on neurologic evaluation and computed tomographic (CT) findings. Patients with a history of stroke, subtentorial signs and symptoms, or alteration of the level of consciousness on admission were excluded from our study.

Within 6 hours after the onset of symptoms all patients underwent neurologic examination, brain CT scan, cerebral angiography, and SPECT study of CBF. SPECT was performed an average of 122.8 (range 60–270) minutes after CT and an average of 60.8 (range 20–210) minutes after the beginning of angiography. Patients were given standard therapies, including antiedema therapy (mannitol), according to their clinical status as necessary.
Neurologic status was evaluated daily for up to 1 month or until death and graded according to the Canadian Neurological Scale (CNS). The degree of neurologic impairment on admission was classified as mild (CNS score of >6.5) or severe (CNS score of <6.5). A CNS score of <6.5 at 1 month was considered a poor outcome since such patients are not self-sufficient.

Brain CT was repeated after 1 week and after 1 month. All patients had ischemic strokes in the middle cerebral artery (MCA) territory. The extent of parenchymal brain damage was evaluated on 1-month follow-up CT scans. Hypodense lesions of >3 cm maximum diameter were classified as large lesions.

Cerebral angiography was performed by the arterial injection of a nonionic contrast medium and the digital subtraction technique. Patients with internal carotid artery (ICA) or MCA occlusion were considered to have a good collateral blood supply if the vessels distal to the occlusion were fully visualized through cortical anastomoses ≤5 seconds after the end of the intracarotid injection of contrast medium. Cerebral blood flow (CBF) was assessed using technetium-99m-labeled hexamethylpropyleneamine oxime ([99mTc]HM-PAO) SPECT on admission and again after 1 week and 1 month by injecting a bolus of 10-15 mCi of [99mTc]HM-PAO intravenously and recording brain views after 10 minutes using a rotating gamma camera (400 T, General Electric, Milwaukee, Wisconsin) equipped with a high-sensitivity collimator. For each CBF study, we recorded 4-5 million counts for a 360° rotation around the head with 64 angular views. The rotation time was 20-30 minutes. After reconstruction and correction for attenuation, we obtained a complete set of axial tomographic slices from the posterior fossa up to the vertex. The slices were 1.2 cm thick and the spatial resolution was 2.5 cm full-width half-maximum.

We chose the SPECT slice showing the greatest asymmetry of perfusion for analysis. Three regions of interest (ROIs) 4x4 pixels (2.5x2.5 cm) in size were placed according to the vascular territories, one ROI each for the anterior cerebral artery, MCA, and posterior cerebral artery territories. The ROI placed in the MCA territory was located over the area of maximum CBF decrease. The ROIs in the unaffected hemisphere were placed symmetrically to those in the affected hemisphere. Two asymmetry indexes (AIs) were then calculated. The interhemispheric AI was calculated by dividing the mean hemispheric CBF value of the affected side by that of the contralateral one, and the regional AI was calculated by dividing the CBF of each ROI in the affected side by that of the homologous ROI in the contralateral hemisphere. For each patient, we considered the regional AI showing the highest value at the admission CBF study. The degree of regional CBF impairment was designated as mild (AI of <40%) or severe (AI of >40%).

Results

On admission, nine patients had a CNS score of >6.5 and the other 23 patients had a CNS score of <6.5. After 1 month, 14 patients had a CNS score of <6.5 and six had died. Therefore, clinical outcome was poor in 20 patients. Of the 23 patients with severe neurologic impairment on admission, 18 had a poor outcome, while seven of the nine patients with mild neurologic impairment on admission had a good outcome. The predictive value of the CNS score on admission was 78% (Figure 1).

Eleven of the 12 patients with severe regional CBF impairment on admission had a poor outcome (predictive value of 92%), while only 11 of the 20 patients with mild regional CBF impairment on admission had a good outcome (predictive value of 55%) (Figure 2). All 10 patients who had a CNS score of <6.5 and an AI of >40% on admission (Figure 3, group I) had a poor outcome. Six of the seven patients with a CNS score of >6.5 and an AI of <40% on admission (Figure 3, group III) had a good outcome. Finally, of the 15 patients with a neurologic status and regional CBF asymmetry mismatch on admission (Figure 3, group II), 11 had a poor outcome and four had a good outcome.
TABLE 1. Early Cerebral Blood Flow Asymmetries According to Computed Tomographic Findings at 1 Month for 26 Patients With Ischemic Stroke

<table>
<thead>
<tr>
<th>Hypodense area at 1 month</th>
<th>n</th>
<th>Interhemispheric</th>
<th>Regional</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or small area</td>
<td>15</td>
<td>-9.8±5.8</td>
<td>-19.1±13</td>
</tr>
<tr>
<td>Large area</td>
<td>11</td>
<td>-26.6±12.8*</td>
<td>-48.6±18.7*</td>
</tr>
</tbody>
</table>

Data are mean±SD.
*<p>0.001 different from small area by Student's unpaired t test.

CT scan, and CT scans remained without a detectable lesion in three patients. Among the 23 patients with a positive CT scan, the hypodense area involved the cortical regions in eight and the cortico-subcortical regions in the other 15. Eleven patients had a large hypodense lesion on follow-up CT scans, and the remaining 15 patients (including the three with normal follow-up CT scans) had small lesions. Interhemispheric and regional AIs were significantly higher in those with large lesions than in those with small lesions (Table 1). Among the eight patients with a normal admission CT scan who developed a large hypodense area on a follow-up scan, seven (88%) had a regional AI of >40% on admission. Among the 11 patients with a normal admission CT scan who developed a small lesion, 10 (91%) had a regional AI of <40% on admission.

According to the angiographic findings, 10 patients had an ICA occlusion, 16 had an MCA occlusion, and six had no occlusion. Regional AI on admission was significantly greater in patients with ICA or MCA occlusion than in patients with no occlusion (Figure 4). All patients with a regional AI of >40% had an ICA or MCA occlusion (Figure 4).

A good collateral blood supply was detected angiographically in 17 of the 26 patients with occlusions. This finding was correlated with interhemispheric and regional AIs indicating mild impairment (Table 2).

At the 1-week follow-up, SPECT showed a significant improvement in regional AI (/>.001) regardless of clinical outcome (Figure 5). There were no significant changes in interhemispheric or regional AIs between 1 week and 1 month (Figure 6).

In four patients, a transient significant (12%) increase in regional AI over the lesion detected at 1 week had disappeared by 1 month. These patients showed a good outcome.

Discussion

The SPECT technique measures relative concentrations of a radioactive tracer within an organ as ratios between two ROIs. Nevertheless, many authors have shown that the semiquantitative SPECT technique provides useful information in different clinical circumstances, particularly stroke.\(^{21-24}\) \[^{99m}Tc\]HM-PAO has a cerebral uptake proportional to CBF,\(^{18,20}\) but no tracer's model has been validated in ischemic tissue so far. Many factors, such as pH, the partition coefficient, and metabolic degradation, affect the distribution of \[^{99m}Tc\]HM-PAO. Moreover,
other technical limitations of SPECT, such as poor resolution, a partial volume effect, and head repositioning, could have affected our results. An additional factor possibly influencing AI is contralateral cerebral diaschisis. We should also consider that our patients, selected according to specific inclusion criteria, may not be representative of acute stroke patients in general. In spite of these limitations, we show that an early severe decrease in CBF, readily detected with SPECT, is highly predictive (92%) of a poor neurologic outcome.

Alteration of the level of consciousness is the most sensitive clinical prognostic factor in predicting poor outcome in stroke patients.26-28 However, an altered level of consciousness is very rare ≤4 hours after the onset of ischemic MCA-territory stroke,14 which makes it less relevant statistically. On the other hand, a CNS score of <6.5 on admission predicted poor clinical outcome in 78% of our patients. We emphasize that severe impairment of both neurologic status and CBF was a constant prognostic factor of poor outcome in this study and may be useful in planning clinical trials of stroke.

The fact that previous SPECT studies have failed to demonstrate a correlation between CBF and clinical outcome when performed later than 6 hours after

Table 2. Early Cerebral Blood Flow Asymmetries According to Collateral Blood Supply in 26 Patients With Angiographic Occlusion

<table>
<thead>
<tr>
<th>Collateral blood supply</th>
<th>n</th>
<th>Interhemispheric</th>
<th>Regional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>17</td>
<td>-18.0±9.4</td>
<td>-32.0±14.7</td>
</tr>
<tr>
<td>Poor</td>
<td>9</td>
<td>-34.7±17.3*</td>
<td>-53.6±20.8*</td>
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Data are mean±SD.
*p<0.005 different from Good by Student's unpaired t test.
the onset of symptoms indicates the existence of a time window after ischemic stroke wherein CBF is a useful factor in predicting outcome. We would define this as the flow-predictive time window. Experimental data support this latter statement. The lack of a correlation between clinical outcome and CBF assessment later than the first few hours after onset is probably due to postischemic hyperemia (absolute or relative luxury perfusion) caused by spontaneous recanalization of occluded vessels. Therefore, CBF has a poor prognostic value >6 hours after the onset of ischemic stroke.

Early recanalization may also affect the predictive value of CBF during the very acute phase of ischemic stroke. In our study early reperfusion could, at least partially, explain the low predictive value of mild CBF impairment regarding good outcome. Our data also agree with PET studies that indicate a CBF threshold below which the outcome of stroke patients is usually poor or the tissue is no longer viable. Factors such as the duration and degree of subthreshold CBF may combine to determine final outcome.

In agreement with Paulson, we found that patients with no detectable arterial occlusion showed a significantly smaller perfusion deficit than patients with ICA or MCA occlusions. Perfusion deficits in patients with ICA occlusions were more severe than in those with MCA occlusions. A good collateral blood supply documented angiographically was accompanied by a minor perfusion impairment. These data are in agreement with a previous report showing that collateral circulation during the first few hours after an ischemic stroke reduced the volume of final parenchymal brain damage.

As previously reported, a perfusion deficit appears on SPECT before morphologic abnormalities appear on CT. Our data support the possibility that a CBF study may predict morphologic damage. In fact, we observed an early severe impairment of regional CBF (AI of >40%) in 88% of the patients who developed a large hypodense area on follow-up CT scan, while an early mild impairment of regional CBF was evident in 91% of those developing small lesions.

In conclusion, the early evaluation of CBF with SPECT appears feasible in a clinical setting aimed at intensive treatment of patients with ischemic stroke during the first hours after onset. Despite limitations of the semiquantitative SPECT method used, our data show that CBF is a reliable predictor of poor outcome early after a stroke. In particular, a severe impairment of CBF predicted patients with a poor outcome. In addition, the evaluation of regional CBF provides information about the persistence of occluded arteries and the volume of final parenchymal brain damage. More subtle clinical correlation may be obtained using a SPECT device with better resolution or new tracers for CBF and cerebral metabolism or by making PET studies available on admission.

Acknowledgments

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References

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**KEY WORDS** • cerebral blood flow • cerebral infarction • tomography, emission computed
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