Detection of Misery Perfusion With Split-Dose 123I-Iodoamphetamine Single-Photon Emission Computed Tomography in Patients With Carotid Occlusive Diseases

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**Background and Purpose**—Patients with carotid occlusive disease and stage 2 cerebral hemodynamic failure, characterized by an increased oxygen extraction fraction (OEF) as measured by positron emission tomography (PET) and otherwise known as misery perfusion, have a high risk of cerebral ischemia and subsequent stroke. In clinical practice, the detection of patients with misery perfusion through the use of widely available, noninvasive, and cost-effective modalities such as single-photon emission computed tomography (SPECT) is extremely important.

**Methods**—We evaluated the relationships between the regional hemodynamic status of cerebral circulation, measured with split-dose [123I] N-isopropyl-p-iodoamphetamine SPECT (123I-IMP SPECT) and an acetazolamide challenge, and hemodynamic parameters, including OEF measured with PET, in 27 patients with both unilateral and bilateral carotid occlusive diseases.

**Results**—A significant negative correlation was found between the SPECT-measured cerebrovascular reserve after acetazolamide administration and both the PET-measured OEF and cerebral blood volume. Neither the cerebrovascular reserve nor the cerebral blood flow index, when expressed as a SPECT-measured cerebrum-to-cerebellum ratio, was useful for detecting lesions with an elevated OEF. However, a combination of the cerebrovascular reserve and cerebral blood flow index showed high sensitivity, specificity, and positive predictive value for the detection of misery perfusion.

**Conclusions**—Our study suggests that split-dose 123I-IMP SPECT with an acetazolamide challenge could be useful for screening patients with misery perfusion in carotid occlusive diseases. (*Stroke*, 2002;33:2217-2223.)

**Key Words:** acetazolamide ■ hemodynamics ■ tomography, emission computed

Severe atherosclerotic disease of the carotid and vertebral arteries or their intracranial branches may cause hemodynamic impairment of the distal cerebral circulation. Several studies have shown that patients with hemodynamics have a high risk of subsequent ischemic stroke1–3; therefore, the identification and treatment of high-risk patients could help to prevent stroke. Among the various methods of hemodynamic assessment, positron emission tomography (PET) is the most reliable tool for the quantitative assessment of blood supply and metabolic demand. When PET with 15O gases is used, the hemodynamic effect can be categorized into 3 stages: stage 0, normal cerebral hemodynamics; stage 1, autoregulatory vasodilatation in which the cerebral blood volume (CBV) is increased and other parameters are normal; and stage 2, in which the cerebral blood flow (CBF) is reduced and the oxygen extraction fraction (OEF) is increased to maintain the cerebral metabolic rate of oxygen (CMRO₂) and CBV.4 Stage 2 has been called “misery perfusion” and represents an inadequate blood supply relative to metabolic demand.5 The presence of an increased OEF lesion can be a predictor of subsequent ischemic stroke.2,3 In clinical practice, the detection of misery perfusion in patients with carotid occlusive disease is important for the prevention of stroke and may be performed with widely available, noninvasive, and cost-effective modalities such as single-photon emission computed tomography (SPECT). However, the conventional method of measuring cerebrovascular reserve (CVR) with SPECT takes >2 days to perform and requires arterial blood sampling. We have developed a split-dose [123I] N-isopropyl-p-iodoamphetamine ([123I]-IMP) SPECT method, followed by an acetazolamide (ACZ) challenge, that enables noninvasive and semiquantitative measurements of regional CBF and CVR to be performed in 1 hour.6,7 Although several studies have shown a relationship between impaired CVR measured...
by ACZ injection or CO₂ inhalation with SPECT and an increased OEF measured by PET, it remains unsettled as to whether an ACZ challenge and split-dose 123I-IMP SPECT can be used to detect patients with misery perfusion. Therefore, the purpose of this study was to clarify the relationship between the CVR and CBF index measured by routine split-dose 123I-IMP SPECT and the hemodynamic parameters measured by PET in 27 carotid occlusive diseases.

**Subjects and Methods**

Enrollment in this study began on February 16, 2000, and ended on July 10, 2001. A total of 43 consecutive patients with chronic cerebrovascular diseases were examined with both SPECT and PET during this period at the Osaka University Medical School Hospital. Before the SPECT and PET examinations, each subject underwent neurological and neuroradiological evaluations, including an evaluation for occlusive cerebrovascular disease by duplex carotid ultrasoundography, MRI, MR angiography (MRA), and cerebral angiography. The MRI examination was performed in 5-mm-thick sections along the orbitomeatal plane with a 1.5-T unit. Infarction was defined as a focal area with prolonged T1 and T2 relaxation times. The interval between the MRI study and the SPECT and PET studies was 30 days. The SPECT study was performed at least 4 weeks after the patient’s most recent clinical episode, once the neurological condition had stabilized. Two neuroradiologists who were unaware of the patients’ medical histories and diagnoses independently reviewed the MRI, SPECT, and PET images. A cerebral angiography was performed in all patients. The maximum percentage of stenosis and the presence of ulceration were evaluated according to the recommendations of the North American Symptomatic Carotid Endarterectomy Trial.

The mechanism of stroke was clinically diagnosed in each patient and classified according to the National Institute of Neurological Disorders and Stroke classification of cerebrovascular disease. Patients with cardioembolic infarctions were excluded from the study. Finally, we selected 27 consecutive patients (13 men, 14 women; mean age, 61.5 ± 12.1 years) with occlusion or stenosis of the internal carotid artery or the main trunk of the middle cerebral artery (MCA) to be included in this study. Fifteen patients had a small cerebral infarction (≤15 mm in diameter), 7 had transient ischemic attacks, and 5 had asymptomatic carotid artery disease. The clinical feature, angiographic findings, and MRI findings are summarized in the Table.

**SPECT Imaging**

We used a high-performance, 4-head rotating gamma camera equipped with a low-energy, general-purpose, parallel-hole collimator with a spatial resolution of 13.0-mm full width at half-maximum (Gamma View SPECT 2000H, Hitachi Medical Co). Data were acquired in a continuous rotating mode in reciprocal directions at 20 seconds per revolution for 66 minutes from 96 directions in a 64×64 matrix. The transaxial images were reconstructed with a Butterworth

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**Table: Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Neurological Deficits</th>
<th>Disease</th>
<th>Angiographical Findings</th>
<th>MRI Findings</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>M</td>
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<td>Asymptomatic</td>
<td>R ICAS</td>
<td>R BG</td>
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<tr>
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<td>CI</td>
<td>R MCAO</td>
<td>R BG—CR</td>
</tr>
<tr>
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<tr>
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<td>73</td>
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<td>L ICAS</td>
<td>R temporal—occipital sub cortex</td>
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<td>6</td>
<td>59</td>
<td>M</td>
<td>L sensory disturbance</td>
<td>TIA</td>
<td>R MCAS, &amp; L ICAS</td>
<td>Bil BG—deep white matter</td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>M</td>
<td>Syncpoe</td>
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<td>R ICAO</td>
<td>Bil BG</td>
</tr>
<tr>
<td>8</td>
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<td>L BG</td>
</tr>
<tr>
<td>9</td>
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<td>Bil deep white matter</td>
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<td>CI</td>
<td>L MCAS</td>
<td>L CR</td>
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</tr>
<tr>
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<td>Bil ICAS</td>
<td>R BG</td>
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<td>L BG</td>
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<tr>
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<td>L BG, L frontoparietal sub cortex</td>
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<tr>
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<td>R BG</td>
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<td>TIA</td>
<td>L MCAS</td>
<td>Pons</td>
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<td>CI</td>
<td>L MCAO, R ICAS</td>
<td>Bil BG</td>
</tr>
<tr>
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<td>L hemiparesis</td>
<td>CI</td>
<td>R ICAO</td>
<td>R frontal lobe</td>
</tr>
<tr>
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<td>R hemiparesis</td>
<td>CI</td>
<td>R ICAO</td>
<td>L BG</td>
</tr>
<tr>
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<td>L hemiparesis</td>
<td>TIA</td>
<td>R ICAO</td>
<td>None</td>
</tr>
<tr>
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<td>F</td>
<td>R hemiparesis &amp; motor aphasia</td>
<td>CI</td>
<td>L ICAS</td>
<td>L BG—CR</td>
</tr>
<tr>
<td>25</td>
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<td>L hemiparesis</td>
<td>TIA</td>
<td>R ICAO</td>
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<tr>
<td>26</td>
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<td>L CR</td>
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<tr>
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<td>71</td>
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<td>L hemiparesis</td>
<td>TIA</td>
<td>R ICAO</td>
<td>R temporal, parietooccipital sub cortex</td>
</tr>
</tbody>
</table>

Asymptomatic indicates asymptomatic carotid artery disease; ICAS, internal carotid artery stenosis; BG, basal ganglia; CI, cerebral infarction; MCAO, MCA occlusion; CR, corona radiata; ICAO, internal carotid artery occlusion; TIA, transient ischemic attack; MCAS, MCA stenosis; and Bil, bilateral.
Two perfusion images (resting and ACZ challenge) were obtained before and after ACZ administration. Two perfusion images (resting and ACZ challenge) were obtained with the subtraction technique.

PET Imaging

All patients were scanned with a Headstone V/SET 2400W system (Shimadzu Co, Ltd), which acquires 63 slices with an interslice distance of 3.1 mm. All scans were performed at a resolution of 3.7-mm full width at half-maximum in the transaxial direction and at 5 mm in the axial direction. The patient’s head was fixed in place with a head holder and was positioned with light beams to obtain transaxial slices parallel to the orbitomeatal line. Before the PET study, germanium-68–gallium-68 transmission scanning was performed for 10 minutes for attenuation correction. Images were reconstructed with a reordered-subset expectation maximization algorithm (12 iterations with 4 ordered subsets). For the 15O-labeled gas steady-state method, 15O2 (550 MBq/min) and 15O2 (1300 MBq/min) were inhaled through a mask. The scan time was 9 minutes, and arterial blood was manually sampled from the radial artery 4 times during each scan. The concentration of the radiotracer activity in the whole blood and plasma was measured with a well counter; the arterial blood hematocrit, hemoglobin concentration, PaO2, and PaCO2 were also measured. Inhalation of 2000 MBq 15O and a 9-minute scanning period were used to measure the CBF. Arterial sampling was manually performed 3 times during the scanning, and the radiotracer activity in whole blood was measured. CBF, CMRO2, and OEF were calculated from the steady-state method, and CMRO2 and OEF were corrected according to the CBV. The study protocol was in accordance with the standard ethics guidelines of Osaka University Medical School, and written, informed consent was obtained from all subjects.

Data Analysis

All SPECT and PET data were analyzed with the Dr. View pro5.0 image analysis software system (Asahi Kasei Joho System Co, Ltd) running on a UNIX system and an Indigo 2 station (Silicon Graphics). The region-of-interest (ROI) analysis in this study is illustrated in Figure 2. Circular ROIs, 20 mm in diameter, were placed over the cortex at the levels of the basal ganglia (lower MCA territory), parietal lobe (upper MCA territory), and cerebellar hemispheres in the SPECT and PET images of each patient. To match the slice thickness, the ROIs in each level of the MCA territories were placed over 3 slices (12 mm) on the SPECT images and over 4 slices (12.5 mm) on the PET images. Finally, 108 regions were investigated in 4 patches (4 regions in each patient: right and left, and upper and lower MCA). In the SPECT study, all ROIs generated in the resting image were transferred to the ACZ-challenge image. In the PET study, all of the ROIs generated in the CBF images were transferred to the OEF, CMRO2, and CBV images. The following equation was used to estimate the percentage increase in regional CBF induced by the ACZ challenge in the form of the CVR: CVR equals ACZ challenge SPECT count minus resting SPECT count divided by resting SPECT count. To estimate the resting CBF, the cerebral cortical ROI counts were normalized to those of the cerebellar hemisphere by use of the higher counts, which eliminated any effects of crossed cerebellar diaschisis.

Seven age-matched patients who complained of nonfocal neurological symptom (dizziness or headache) and who showed no ischemic lesions after MRI and no stenotic lesions in their major cerebral arteries after MRA underwent PET examination to determine their control values. The normal control values for CBF and cerebro-to-cerebellum ratio (CBF index) for the MCA territories made a normal distribution; they were 0.69±0.23 and 0.83±0.09, respectively. The mean CBF after ACZ challenge in the normal subjects was 0.69 in our study, which agrees with previous reports.14,15 The CBF index and CVR values were judged to be abnormal when they were beyond the range of the mean±2 SD range of the normal control subjects. The 108 MCA territories examined were divided into 2 groups according to the angiographic findings. Group A consisted of MCA areas with a severe stenotic lesion (>70%) in the ipsilateral internal carotid artery system, whereas group NA consisted of those with less or no stenotic lesion. All regions were also classified into 2 groups according to their SPECT CVR values: a reduced CVR group with a CVR of >0.23 (mean –2 SD) and a normal CVR group with a CVR of ≥0.23. Because normal OEF values obtained from healthy control subjects were not available, we used PET parameter values obtained from 7 patients with no infarction and no severe stenosis or occlusion (<50%) who were suffering from nonspecific brain symptoms without focal signs (ie, preoperation for cerebral aneurysm, headache, dizziness, and syncope) as the normal values: CBF, 46.9±11.3 mL · 100 g−1 · min−1 (mean±SD); OEF, 44.1±4.62%; CMRO2, 3.39±0.82 mL · 100 g−1 · min−1; and CBV, 4.22±0.75%. All regions were classified into 3 groups on the basis of their OEF values: normal group, OEF <48.7%; mean ±1 SD of the mean OEF value; slightly increased OEF group, 48.7% ≤ OEF <53.3% (mean ±2 SD of the mean OEF value); and an increased OEF group, OEF ≥53.3%. The increased OEF value was compatible with that beyond the upper 95% confidence limits defined in healthy volunteers.3 We assessed the relationship between the SPECT and PET parameters in the MCA territories using linear
regression analysis and Pearson’s correlation coefficient. All data are expressed as mean±SD. Differences in data between groups were statistically evaluated with an unpaired t test. Differences with values of P<0.05 were considered to be statistically significant.

Results
Comparison of SPECT and PET Parameters
Of the 108 ROIs in all MCA territories, 64 ROIs were on an affected side (group A), and 44 ROIs were on a nonaffected side (group NA), because 5 patients with bilateral carotid disease were included. We compared the CVR and PET parameters in group A and found a significant negative correlation between CVR and OEF (r = −0.549, P<0.0001; Figure 3) and between CVR and CBV (r = −0.313, P<0.0117; Figure 3). CBF and CMRO 2 were not correlated with the CVR (Figure 3).

Detection of Stage 2 Cerebral Hemodynamic Failure With Semiquantitative SPECT Analysis in Group A
Figure 4 shows the typical MRI, MRA, SPECT, and PET images of a stage 2 patient. The areas of increased OEF and CBV (misery perfusion) on the PET images correspond with those of decreased CVR on the SPECT images. The lesions were classified into 3 groups according to their PET-evaluated OEF values, and each value was plotted according to the CBF index at rest and the CVR values obtained in the SPECT study (Figure 5). When the CVR cutoff value was set at 0.23 (mean±2 SD; broken line), the sensitivity of the measurement was 82% (9 of 11), the specificity was 96% (51 of 53), and the positive predictive value was 82% (9 of 11).

Discussion
Because stage 2 cerebral hemodynamic failure, characterized by an elevated OEF and also known as misery perfusion, significantly increases the risks of stroke and ipsilateral ischemic stroke,2,3 patients with misery perfusion must be detected in clinical practice through the use of widely available modalities such as SPECT. However, a single measurement of CBF alone with SPECT is insufficient to assess the cerebral hemodynamic status in patients with carotid occlusive diseases. Therefore, CVR is usually assessed by paired blood flow measurements, with the initial measurement performed at rest and the second measurement performed after a vasodilatory stimulus such as hypercapnia, an ACZ challenge, or physiological tasks. Although a dissociation between the CBF response to hypercapnia, ACZ, or neural activation has been reported in patients with carotid occlusive disease,16,17 ACZ increases the arterial-to-capillary blood volume and CBF without changing the CMR O 2 and other physiological parameters. 18 Only a few studies have investigated the relationship between ACZ reactivity and OEF.10,11 Some investigators have reported no significant relationship between O 15 H 2 O PET-measured changes in CBF after an ACZ challenge and quantitative OEF values.19 Conversely, the most consistent results have been published by Hirano et al,10 who reported that a reduced regional CVR on IMP SPECT was strongly correlated with an elevated OEF and suggested that a significantly reduced regional CVR represents stage 2 hemodynamic failure with an increased OEF on PET. Hirano et al used conventional 123I-IMP SPECT with arterial sampling and an asymmetry index comparing affected and nonaffected sides after the ACZ test. However, cerebral hemodynamics may be disturbed in the nonaffected hemisphere as a result of collateral circulation, suggesting that the CVR in the contralateral hemisphere cannot be used as an internal control for each patient, even in unilateral hemorrhage.
carotid occlusive disease. Furthermore, patients with bilateral carotid disease cannot be evaluated with an asymmetry index for 123I-IMP SPECT after an ACZ challenge.

We have developed a split-dose 123I-IMP SPECT method for evaluating CVR after cerebral vasodilatory stimuli and have modified the procedure so that invasive arterial blood sampling is not required. In contrast to the conventional 123I-IMP SPECT method for measuring CVR, which required arterial sampling and 2 days to perform, our split-dose 123I-IMP SPECT method can be completed in ≈1 hour. During the short interval between the baseline and ACZ challenge tests, the physiological parameters (blood pressure, arterial pH, and PaCO₂) should be stable, allowing the absolute CVR values to be calculated without arterial blood sampling for quantitative measurement of CBF.

In contrast to Powers’ theory, a negative correlation was observed between split-dose 123I-IMP SPECT–measured CVR values and the OEF, suggesting that the OEF may be elevated even at the stage when the CVR response to ACZ is maintained. Several factors may contribute to this correlation between CVR and OEF. First, the OEF may begin to increase before the arteries reach maximal dilatation by autoregulation. This is supported by Derdeyn et al., who observed patients with an increased OEF but without an increased CBV. Second, the vascular systems that dilate after a decrease in cerebral perfusion pressure or in response to an ACZ...
Figure 5. Detection of stage 2 cerebral hemodynamic failure by semiquantitative SPECT analysis on the affected side (group A). The lesions were classified into 3 groups according to their OEF values determined by PET, and each value was plotted on the basis of the CVR at rest and CVR measured in the SPECT study. Neither the CBF index nor CVR alone was effective in detecting lesions with an elevated OEF. However, when a CVR cutoff value of 0.23 (mean–2 SD; broken line) and a CBF index cutoff value of 0.83 (normal value; thick line) were combined, a sensitivity of 82% (9 of 11), specificity of 96% (51 of 53), and a positive predictive value of 82% (9 of 11) were obtained.

On the basis of the correlation between the split-dose $^{123}$I-IMP SPECT–measured CVR and PET-measured OEF values, we attempted to clarify whether the CVR value alone could predict the existence of misery perfusion. Although the CVR cutoff value showed a high sensitivity (10 of 11, 91%) for the detection of misery perfusion (Figure 5), the positive predictive value was rather low (10 of 19, 53%). Because a significant correlation between CVR and CBF was not found in the PET study (Figure 3), we used the $^{123}$I-IMP SPECT–measured CBF index as a cerebrum-to-cerebellum ratio to improve the positive predictive value of CVR for detecting misery perfusion. The SPECT–measured CBF index and the PET-measured CBF values were significantly correlated ($r=0.380, P<0.001$; data not presented). As expected from the results of Figure 3, the CBF indexes in ROIs below the CVR cutoff value (0.23) varied considerably (from 0.43 to 1.11). However, a combined CVR cutoff value (0.23) and a CBF index cutoff value of 0.83 produced a high sensitivity (9 of 11, 82%), specificity (51 of 53, 96%), and positive predictive value (9 of 11, 82%) for the detection of misery perfusion with an increased OEF (OEF >53.3%), as shown in Figure 5. We determined an abnormal CVR and CBF index with a 95% confidence limit from control subjects in the present study on the basis of the previous studies$^{8,10,20}$; however, the pathophysiological relevance of a CVR and CBF index that is 2 SD from the mean is not necessarily clear and should be clarified in future studies. Five patients with bilateral carotid occlusive diseases were included in this study (the Table), but none of these patients exhibited an elevated OEF on their PET images. However, the combination of the CVR and CBF index (Figure 5) could potentially be applied for the detection of misery perfusion in both unilateral and bilateral carotid occlusive diseases.

In conclusion, split-dose $^{123}$I-IMP SPECT can be potentially useful as a cost-effective, noninvasive tool to detect patients with misery perfusion. The combination of the CVR and CBF index can be a reliable index for accurately detecting the existence of increased OEF in both unilateral and bilateral carotid occlusive diseases.

References
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