Background and Purpose—Severe atherosclerotic disease of the carotid arteries may affect perfusion in the posterior circulation according to the degree of collateral supply. The purpose of this study was to determine whether the responses of regional cerebral blood flow (rCBF) and regional cerebral metabolic rate of oxygen (rCMRO₂) during neural stimulation are affected by the baseline perfusion or oxygen metabolism.

Methods—We used PET to measure rCBF, rCMRO₂, and regional oxygen extraction fraction (rOEF) in 13 patients with carotid artery steno-occlusive lesions at baseline and during visual stimulation. We examined whether the changes in CBF, CMRO₂, and OEF during visual stimulation were correlated with the baseline values of these parameters in the visual cortex.

Results—With visual stimulation, rCBF increased in all patients, whereas rCMRO₂ showed variable changes. The baseline rCMRO₂ value showed a positive relationship with the degree of rCBF increase and a negative relationship to the degree of rCMRO₂ increase. rCMRO₂ decreased in patients with relatively high baseline rCMRO₂ values, resulting in dissociation of the rCMRO₂ response from the rCBF response. The rCBF increase was large in the region with an increased baseline rOEF value. These variable changes in rCBF and rCMRO₂ resulted in a significant correlation between the values of rCBF and rCMRO₂ during visual stimulation in contrast to the lack of such a correlation at baseline.

Conclusions—In patients with cerebrovascular disease, neural stimulation may induce variable changes in rCBF and rCMRO₂ according to the baseline perfusion and oxygen metabolism. (Stroke. 2002;33:1294-1300.)

Key Words: carotid artery diseases | cerebral blood flow | oxygen | tomography, emission-computed
artery disease. The abnormal response in some patients with normal cerebral hemodynamics suggested that hemodynamic disturbance is not the sole determinant of the abnormal rCBF response. When the diseased cerebral arteries perfuse the activated region, the possibility of the abnormal rCBF response caused by ischemic tissue damage of the activated region cannot be excluded completely, which might complicate the interpretation of results. The responses of rCMRO₂ during activation in cerebrovascular disease are also largely unknown. Indirectly, a study with near-infrared spectroscopy showed variable oxyhemoglobin and deoxyhemoglobin responses to language activation in patients with stroke, suggesting the multiplicity of the rCBF and rCMRO₂ responses to neuronal activation. FMR1 studies of normal children have suggested that the degree of increase in rCBF relative to the increase in rCMRO₂ during neural activation in the visual cortex may be affected by changes in baseline metabolism during development. These studies suggest that changes in baseline perfusion or metabolism in cerebrovascular disease may cause complex changes in rCBF and rCMRO₂ during neural activation.

In this study, we used PET to quantitatively measure rCBF and rCMRO₂ at rest and during visual stimulation in the visual cortex of patients with carotid artery steno-occlusive lesions, and we examined the relationship of the changes in rCBF and rCMRO₂ to the baseline values of these parameters and rOEF. To minimize the effect of direct ischemic tissue damage on the changes of rCBF and rCMRO₂ during activation, we selected patients with carotid artery steno-occlusive lesions in whom ischemic damage of the visual cortex is less likely and chose visual stimulation as the neuronal activation task. On the other hand, the visual cortex in these patients may show a variable degree of perfusion disturbance (changes in rCBF and rOEF) or metabolic decline (changes in rCMRO₂) according to the degree of collateral supply from the posterior circulation to the anterior circulation or secondary metabolic depression from ischemic damage in the diseased carotid artery territory. The visual activation used in this study can induce large rCBF and rCMRO₂ changes, which should be sufficient to permit correlational analysis among the responses. The purpose of this study was to determine whether neural stimulation induces variable changes in rCBF and rCMRO₂ according to the baseline perfusion or oxygen metabolism in cerebrovascular disease.

Subjects and Methods

Patients

We studied 13 patients with angiographically documented occlusion or stenosis (>70% diameter reduction) of the common carotid artery (CCA) or internal carotid artery (ICA). These patients included 9 men and 4 women who were 49 to 78 years of age (mean±SD, 56±9 years). Three patients had no symptoms, 1 had a transient ischemic attack, and 9 had had minor hemispheric stroke with mild disability. All symptoms were related to the affected carotid artery distribution, and no patient had visual symptoms. In the 10 symptomatic patients, the interval between the last ischemic event and PET evaluations ranged from 1 to 36 months (mean±SD, 9±13 months). All patients had normal visual acuity and visual field. In the asymptomatic patients, arterial disease was suspected because of findings on echo angiograms performed as part of the screening for cerebral arterial disease concomitant with coronary arterial disease. MRI disclosed no cortical infarctions and at most only 1 infarction <1.5 cm in diameter. No abnormality was found in the primary visual cortex or in the white matter corresponding to the optic radiation. In the 3 asymptomatic patients and 1 patient with transient ischemic attack, MRIs were normal. In each of the 9 stroke patients, patchy or confluent high-intensity areas were observed in the affected cerebral white matter on T2-weighted MRI. A smaller degree of abnormality was found on the nonaffected side in 6 patients. Most of these abnormalities were undetectable on T1-weighted MRI, which showed at most only minor subcortical abnormalities in the affected ICA territory. Conventional angiography revealed unilateral ICA occlusion in 4 patients, unilateral extracranial ICA stenosis (75% and 80%) in 2 patients, unilateral CCA stenosis (70%, 80%, and 90%) in 3 patients, bilateral extracranial ICA stenosis (80/70% and 70/50%) in 2 patients, and ICA occlusion with contralateral extracranial ICA stenosis (80% and 50%) in 2 patients. In 3 symptomatic patients with bilateral disease, only the side with more severe vascular lesions was symptomatic. One patient with ICA occlusion with contralateral ICA stenosis had a recent origin of the posterior cerebral artery from the stenosed ICA. Collateral pathways from the posterior circulation to the anterior circulation were present in 7 patients and included a leptomeningeal anastomosis between the posterior cerebral artery and the middle cerebral artery in 3 patients, a posterior communicating artery in 2, and both in 2. No significant disease of the posterior cerebral artery was seen in any patient. Two patients showed reversal of flow of 1 vertebral artery because of stenosis of the right brachiocephalic artery or the left subclavian artery, but the vertebrobasilar system was angiographically normal in the other 11 patients. The intervals between the conventional angiography and PET studies ranged from 3 to 30 days (mean 18±12 days). In the asymptomatic patients, ICA occlusion was confirmed on angiography ≤1 month before the PET study. Four patients had a history of hypertension, 3 others had a history of diabetes mellitus, and 2 others had a history of both. We also studied 8 normal volunteers (3 men, 5 women) who were 24±4 years of age (mean±SD) as younger control subjects. These subjects showed normal neurological findings and no specific neurological diseases. None exhibited any abnormal MRI findings, except for a few punctate high-intensity areas in the subcortical white matter on T2-weighted images without corresponding abnormality on T1-weighted images. None of them had hypertension or diabetes mellitus.

PET Measurements

All subjects underwent PET scans with the whole-body Advance PET scanner (General Electric Medical System), which permits simultaneous acquisition of 35 image slices in a 2- or 3-dimensional acquisition mode with interslice spacing of 4.25 mm. Written, informed consent was obtained from each subject under the guidance of the Ethics Committee of the Shiga Medical Center. Performance tests showed the intrinsic resolution of the scanner to be 4.6 to 5.7 mm in the transaxial direction and 4.0 to 5.3 mm in the axial direction. As part of the scanning procedure but before the tracer administration, ⁴⁰Ge/⁶⁸Ga transmission scanning was performed for 10 minutes for attenuation correction. For reconstruction of PET data, images were blurred to 6.0-mm full-width-half-maximum in the transaxial direction with a Hanning filter. Functional images were reconstructed as 128×128 pixels, with each pixel representing a 2.0×2.0-mm area.

The subjects were positioned in the scanner with their heads immobilized with a head holder and positioned with light beams to obtain transaxial slices parallel to the orbito-meatal line. A small cannula was placed in the left brachial artery for blood sampling. After intravenous bolus injection of 555 MBq of H₂¹⁵O into the right antebrachial vein, a 3-minute dynamic PET scan was started at the time of tracer administration with frame durations of 5 seconds for 12 frames, 10 seconds for 6 frames, and 20 seconds for 3 using the 3-dimensional mode. In the oxygen bolus inhalation method, the same procedure of dynamic PET acquisition was started at the time of bolus inhalation of ⁴¹O₂ at an amount up to 1800 MBq. Arterial blood was continuously drawn from a catheter in the radial artery.
TABLE 1. Physiological Data Obtained in the Baseline and Activation Conditions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Baseline</th>
<th>Patients Activation</th>
<th>Control Subjects Baseline</th>
<th>Control Subjects Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit, %</td>
<td>39.2±3.8</td>
<td>39.2±4.0</td>
<td>38.6±4.0</td>
<td>38.6±4.0</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.7±1.2</td>
<td>12.8±1.3</td>
<td>12.5±1.3</td>
<td>12.5±1.3</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>37.9±3.2</td>
<td>37.8±3.0</td>
<td>39.6±3.3</td>
<td>39.3±3.9</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>83.3±10.3†</td>
<td>89.8±9.9†</td>
<td>103.1±6.7</td>
<td>101.7±4.5</td>
</tr>
<tr>
<td>Cau₀, mL/dL</td>
<td>16.9±1.7</td>
<td>17.1±1.8*</td>
<td>17.0±1.8</td>
<td>17.0±1.8</td>
</tr>
<tr>
<td>MABP, mm Hg</td>
<td>99±14†</td>
<td>100±14†</td>
<td>76±6</td>
<td>74±6*</td>
</tr>
</tbody>
</table>

MABP indicates mean arterial blood pressure. Values are mean±SD.

*P<0.05 vs baseline (paired t test).
†P<0.01 vs control value in the same condition (unpaired t test).

Results

Control Subjects

There was no significant difference in the physiological data obtained in the control subjects during PET scanning at baseline and during visual stimulation, except for a slight decrease in mean arterial blood pressure (Table 1). The values of the correction factor [global value (activation)/global value (baseline)] for CBF, CMRO₂, and OEF were 0.99±0.04, 1.00±0.07, and 1.01±0.05 (mean±SD), respectively. There was no significant difference in global CBF, CMRO₂, or OEF between the baseline and activated conditions.

During visual stimulation, the rCBF values in the visual cortex increased in all patients (mean increase, 28%;
All but 1 patient showed an increase in rCMR O 2 values (mean increase, 4%; P<0.05). The rOEF values were decreased in all patients (mean decrease, 18%; P<0.001). The change in rCMR O 2 was significantly and negatively correlated with the baseline value of rCMR O 2 (r=0.85, P<0.01).

A significant correlation was found between the values of rCMR O 2 and rCBF in the visual cortex at baseline (r=0.79, P<0.01), although there was no such correlation during visual stimulation (r=0.45, P=0.26). A significant negative correlation was found between the changes in rOEF and rCBF (r=-0.86, P<0.01).

Patients

There was no significant difference in the physiological data obtained in patients during PET scanning at baseline and during visual stimulation, except for slight increases in PaO 2 and CaO 2 (Table 1). The values of the correction factor

### Table 2. Baseline and Activation Values of PET Variables in the Visual Cortices Ipsilateral and Contralateral to the More Severe Carotid Artery Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Conditions</th>
<th>Hemisphere</th>
<th>Baseline</th>
<th>Activation</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF, mL · 100 g⁻¹ · min⁻¹</td>
<td>Ipsilateral</td>
<td>43.0±5.1</td>
<td>49.2±6.9</td>
<td>14.5±10.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contralateral</td>
<td>43.0±5.8</td>
<td>50.3±6.6</td>
<td>17.5±11.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>52.1±3.2</td>
<td>66.6±6.0</td>
<td>28.0±9.0</td>
<td></td>
</tr>
<tr>
<td>rCMRO 2, mL · 100 g⁻¹ · min⁻¹</td>
<td>Ipsilateral</td>
<td>4.65±0.52</td>
<td>4.82±0.35</td>
<td>4.1±6.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contralateral</td>
<td>4.74±0.44</td>
<td>4.81±0.37</td>
<td>1.8±5.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>5.25±0.58</td>
<td>5.45±0.43</td>
<td>4.4±4.6</td>
<td></td>
</tr>
<tr>
<td>rOEF, %</td>
<td>Ipsilateral</td>
<td>62.1±7.0</td>
<td>55.6±6.4</td>
<td>-9.8±10.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contralateral</td>
<td>63.5±7.8</td>
<td>54.3±6.9</td>
<td>-14.2±7.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>59.5±6.3</td>
<td>48.9±7.3</td>
<td>-18.1±6.4</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD. The values of rCBF, rCMRO 2, and rOEF during activation were corrected by dividing by the correction factor of each variable: global value (activation)/global value (baseline).

*P<0.05, †P<0.01, ‡P<0.0001 vs baseline (paired t test).

§P<0.05, ||P<0.005 vs control (1-way analysis of variance and post hoc Scheffe’s analysis).

Figure 1. Examples of PET images of rCBF (according to a pseudocolor scale ranging from 0 to 80 mL · 100 g⁻¹ · min⁻¹) (columns 1 and 3) and rCMRO 2 (from 0 to 8.5 mL · 100 g⁻¹ · min⁻¹) (columns 2 and 4) obtained at baseline (row 1) and during visual stimulation (row 2) in 2 patients. Images of rCBF and rCMRO 2 during activation were corrected by dividing by the correction factor of each variable: global values (activation)/global values (baseline). In the patient with left (Lt) CCA stenosis who showed relatively low rCBF and relatively high rCMRO 2 values at baseline, a marked increase in rCBF with a decrease in rCMRO 2 was found during activation. In the patient with right (Rt) ICA occlusion who showed higher rCBF and lower rCMRO 2 values than the other patient at baseline, a smaller increase in rCBF and a small increase in rCMRO 2 were found during activation.
Results

Changes in rCBF, rCMRO₂, and rOEF during visual stimulation were variable among patients. The degree of increase in rCBF did not differ between patients and control subjects. rCMRO₂ decreased in patients with relatively high baseline rCMRO₂ values and increased in patients with low rCMRO₂ values. Thus, dissociation of the rCMRO₂ response from the rCBF response occurred in some patients. In patients, these variable changes in rCBF and rCMRO₂ resulted in a significant correlation between the values of rCBF and rCMRO₂ during visual stimulation in the visual cortex, although there was no such correlation at baseline.

It has been speculated that the rCBF response should be absent in regions with increased rOEF, in which autoregulatory cerebral vasodilation may be maximal in response to reduced cerebral perfusion pressure. In this study, however, visual stimulation increased rCBF in the visual cortex in all patients studied. Furthermore, the increase in rCBF tended to be larger in the region showing increased rOEF at baseline, in contradiction to the speculation. In the patients studied, the increased baseline rOEF may have been caused by carotid artery disease because the visual cortices in patients with severe carotid artery disease.

Discussion

This study showed that in patients with cerebrovascular disease, neural stimulation induces variable changes in rCBF and rCMRO₂ according to the baseline perfusion and oxygen metabolism. In the visual cortex in patients with carotid artery steno-occlusive lesions, visual stimulation increased rCBF in all patients. The degree of increase in rCBF in patients was decreased in the visual cortex ipsilateral to the more severe carotid artery disease compared with the degree of increase in younger control subjects and was positively correlated with the baseline rCMRO₂ value. The decreased rCBF response was associated with an increase but with a decrease in baseline rOEF value (an index of perfusion disturbance). On the other hand, rCMRO₂ showed variable changes among patients. The degree of increase in rCMRO₂ did not differ between patients and control subjects and was negatively correlated with the baseline value of rCMRO₂. Thus, dissociation of the rCMRO₂ response from the rCBF response occurred in some patients. In patients, these variable changes in rCBF and rCMRO₂ resulted in a significant correlation between the values of rCBF and rCMRO₂ during visual stimulation in the visual cortex, although there was no such correlation at baseline.

It has been speculated that the rCBF response should be absent in regions with increased rOEF, in which autoregulatory cerebral vasodilation may be maximal in response to reduced cerebral perfusion pressure. In this study, however, visual stimulation increased rCBF in the visual cortex in all patients studied. Furthermore, the increase in rCBF tended to be larger in the region showing increased rOEF at baseline, in contradiction to the speculation. In the patients studied, the increased baseline rOEF may have been caused by carotid artery disease because the visual cortices in patients with severe carotid artery disease.
severe bilateral carotid artery diseases had a higher rOEF than in patients with unilateral disease. In patients with bilateral disease of the carotid artery, blood flowing through the basilar artery will be redistributed via the posterior communicating arteries and leptomeningeal vessels to compensate for reduced flow in the anterior circulation, resulting in reduced flow in the visual cortex. Therefore, in cerebrovascular disease, neural stimulation can induce an rCBF response, the degree of which does not necessarily decrease because of perfusion disturbance. Indeed, decreased rCBF relative to rCMRO₂ (increased rOEF), if the rCMRO₂ is preserved, may even increase the degree of the rCBF response. Our results are consistent with those of an earlier PET study that showed reduced rCBF responses to physiological stimulation of the sensorimotor cortex independent of baseline hemodynamic disturbance in some patients with severe carotid artery disease in whom rCMRO₂ might be decreased. The rCBF response was decreased only in the visual cortex ipsilateral to the more severe carotid artery disease, where the baseline rCMRO₂ value was decreased compared with that in younger control subjects. This is probably the result of secondary metabolic depression from ischemic damage in the region of the carotid artery distribution or, less likely, primary ischemic changes, although other factors, including age and vascular risk factors, may contribute to the bilateral decrease in baseline rCMRO₂. A recent PET study showed that in unilateral major cerebral arterial occlusive diseases, rCBF increased in both hemispheres with bimanual activation, but only in the contralateral hemisphere with acetazolamide, suggesting that neural activation can induce a nearly normal rCBF response in brains with preexisting vasodilation. It is speculated that the mechanism of vasodilation responsible for activation-induced rCBF change may be different in part from the mechanism of autoregulatory vasodilation. Different mediators or different sizes of arteries may contribute to vasodilation in these 2 conditions. Taken together, these findings indicate that rCBF can increase in response to neural activation in the presence of autoregulatory vasodilation, and an increase in rCBF can be used as a qualitative index of local neuronal activity in cerebrovascular disease.

We made the surprising findings here that the rCMRO₂ response to visual stimulation was negatively associated with baseline rCMRO₂ and that the rCMRO₂ decreased in patients with relatively high baseline rCMRO₂ and increased in patients with low rCMRO₂, although an increase in rCBF suggested increased neuronal activity in all patients. The rCMRO₂ response during neural activation may be affected by the baseline oxygen metabolism and may be dissociated from the rCBF response in cerebrovascular disease. fMRI studies in normal children have suggested that the increase in rCBF relative to the increase in rCMRO₂ during neural activation is dependent on the baseline metabolism. A decrease in rCMRO₂ with an increase in rCBF during activation, which has been reported in a few normal subjects, has not been shown in patients with cerebrovascular disease. However, a study with near-infrared spectroscopy showed a large decrease in deoxyhemoglobin during language activation in some patients with cerebrovascular disease, which might suggest a decrease in rCMRO₂ during neuronal activation. The reason for the rCMRO₂ decrease during activation is unclear. However, a significant correlation between the values of rCMRO₂ and rCBF in the visual cortex was absent at baseline but present during visual stimulation, suggesting that variable changes in rCBF and rCMRO₂ might be induced during activation to attain a certain relationship between rCBF and rCMRO₂ in the activated brain region. Thus, one possible explanation for the rCMRO₂ decrease is that a change in some metabolic components during activation may induce the rCMRO₂ decrease. The primary metabolic change associated with increases in neuronal activity may be an increase in nonoxidative glucose metabolism, which may have occurred in patients with a decrease in rCMRO₂ during neural stimulation in this study. In patients with relatively high baseline rCMRO₂, a certain portion of the oxidative metabolism of glucose occurring at baseline might change into nonoxidative metabolism on stimulation, which may produce an efflux of lactate into the blood circulation without oxygen consumption, leading to a decrease in rCMRO₂. Further studies, including measurements of regional glucose metabolism or definitive measurements of neuronal activity, are required to test this hypothesis.

The bolus method for rCMRO₂ used in this study allows repetition of the measurements every 10 minutes. This method is considered ideal for repeated measurement of rCMRO₂ before and after cerebral activation to see the effect of activation. However, this method may overestimate rCMRO₂ and consequently rOEF in the brain region near the major veins and sinuses. This may be true in the visual cortical region analyzed in this study. Although blood volume was estimated and extracted as a separate parameter in this method, the radioactivity resulting from unextracted ¹⁵O₂ in the venous blood may not be excluded sufficiently. To obtain precise rCMRO₂ and rOEF values with this bolus method, correction for the intravenous unextracted ¹⁵O₂ may be needed. In patients with carotid artery disease, the value of blood volume in the visual cortex may differ according to the degree of autoregulatory vasodilation, and this variation in itself may lead to variation in baseline rCMRO₂ values. The large rCBF increase, probably with a large increase in blood volume, in patients with a rCMRO₂ decrease may eliminate the possibility that an inadequate correction for the intravenous unextracted ¹⁵O₂ may be needed. In patients with carotid artery disease, the value of blood volume in the visual cortex may differ according to the degree of autoregulatory vasodilation, and this variation in itself may lead to variation in baseline rCMRO₂ values. The large rCBF increase, probably with a large increase in blood volume, in patients with a rCMRO₂ decrease may eliminate the possibility that an inadequate correction for the intravenous unextracted ¹⁵O₂ may be needed. Therefore, we cannot completely exclude the possibility that methodological problems may have led to the negative relationship between rCMRO₂ response and baseline rCMRO₂ value.

The multiplicity of rCBF and rCMRO₂ responses to neuronal activation shown in this study has some implications for fMRI studies, with the assumption that similar changes occur after other kinds of stimulation in other cortical areas. Most fMRI studies are based on the blood oxygen level–dependent (BOLD) contrast caused by alterations in local deoxyhemoglobin content, which is indexed by changes in rOEF when CaO₂ is constant. A decrease in rOEF during activation is
associated with an increased BOLD signal. The present study showed that the degree of decrease in rOEF during activation was correlated with the degree of increase in CBF, suggesting that the BOLD signal change can be used as a qualitative index of the rCBF response in cerebrovascular disease. This finding is in agreement with the similarities in activation patterns among PET and fMRI measurements in previous studies and supports the idea that fMRI can be applied to the study of functional localization after stroke. However, the dependence of the decrease in rOEF on baseline rCMRO2 values suggests that the change in baseline oxygen metabolism in stroke patients may affect the degree of BOLD signal change during activation. Thus, caution should be exercised in the interpretation of the change in BOLD signal during activation as a quantitative index of the functional change after stroke.

In conclusion, in patients with cerebrovascular disease and normal visual function, neural stimulation induces an increase in rCBF in the visual cortex regardless of the severity of perfusion disturbance. This supports the idea that functional imaging methods of brain activation can be applied to the study of functional localization after stroke. However, the dissociation of the change in rCMRO2 from the change in rCBF, which may depend on baseline rCMRO2, should be kept in mind when changes in rCBF and rCMRO2 are used as quantitative indexes of brain function. Our quantitative data will be useful for the interpretation of the results obtained from other qualitative functional imaging methods in cerebrovascular disease.

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References
Changes in Blood Flow and Oxygen Metabolism During Visual Stimulation in Carotid Artery Disease: Effect of Baseline Perfusion and Oxygen Metabolism

Hiroshi Yamauchi, Hidehiko Okazawa, Yoshihiko Kishibe, Kanji Sugimoto and Masaaki Takahashi

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