Compensatory Mechanisms for Chronic Cerebral Hypoperfusion in Patients With Carotid Occlusion

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Background and Purpose—The purpose of this experiment was to assess long-term cerebral hemodynamic and metabolic changes in patients with increased oxygen extraction fraction (OEF) in the hemisphere distal to an occluded carotid artery who remain free of stroke.

Methods—Ten patients with increased OEF and no interval stroke underwent repeated positron emission tomography examinations 12 to 59 months after the initial examination. Quantitative regional measurements of cerebral blood flow, cerebral blood volume, cerebral rate of oxygen metabolism (CMRO₂), and OEF were obtained. Regional measurements of the cerebral rate of glucose metabolism (CMRGlc) were made on follow-up in 5 patients. Statistical significance (P<0.05) was measured with t tests and linear regression analysis.

Results—The ipsilateral/contralateral OEF ratio declined from a mean of 1.16 to 1.08 (P=0.022). Greater reductions were seen with longer duration of follow-up (P=0.023, r=0.707). The cerebral blood flow ratio improved from 0.81 to 0.85 (P=0.021). No change in cerebral blood volume or CMRO₂ was observed. CMRGlc was reduced in the ipsilateral hemisphere (P=0.001 compared with normal), but the CMRO₂/CMRGlc ratio was normal.

Conclusions—Increased OEF improves in patients with carotid occlusion and no interval stroke. This improvement in OEF is due to an improvement in collateral blood flow. (Stroke. 1999;30:1019-1024.)

Key Words: blood flow □ carotid artery occlusion □ glucose metabolism □ hemodynamics □ oxygen
metabolism (CMRGlc), raising the possibility that misery perfusion could produce a shift toward more reliance on nonoxidative glycolysis.16

The aim of this study was to assess longitudinally the hemodynamic and metabolic changes that occurred in patients with carotid occlusion and increased OEF who did not suffer subsequent cerebral infarction. We sought to determine whether misery perfusion improved over time and, if so, to determine the mechanism.

**Subjects and Methods**

**Patients**

Positron emission tomography (PET) studies were performed on 10 subjects. All were participants in the St Louis Carotid Occlusion Study (STLCOS), a prospective longitudinal study of the importance of hemodynamic factors in the prognosis of carotid occlusion.6,17

During 1991–1997, 117 patients with symptomatic or asymptomatic carotid artery occlusion were enrolled in STLCOS. From these we selected 10 subjects who met the following criteria: (1) increased OEF in the middle cerebral artery territory distal to the occluded carotid artery;2–7: (2) no ischemic event since study enrollment; (3) initial complete quantitative PET examination (arterial time-activity curve data could not be acquired in some patients); and (4) availability and willingness of the patient to return for follow-up PET examination. Clinical evaluation, including a neurological examination, was performed on all patients returning for repeated PET studies. Current medications were recorded both at initial interview and at the time of follow-up examination.

Two sets of normal control subjects were studied. For the purposes of establishing a range of normal control cerebral hemodynamic and metabolic values, PET measurements of CBF, cerebral blood volume (CBV), and OEF were obtained in 18 normal volunteers aged 19 to 77 years (mean age, 45 years). All volunteers had normal neurological examinations, MR scans of the head, and duplex ultrasound studies of the carotid bifurcation. A second group of normal volunteers (n = 7) was used to establish a normal range for CMRGlc. They ranged in age from 19 to 43 years old (mean age, 26 years). All protocols were approved by the Human Studies Committee and the Radioactive Drug Research Committee of Washington University School of Medicine.

**PET Measurements**

Blood pressure was measured in the clinic before the subject walked to the scanner suite. After the subject was positioned on the scanner gantry, an individually molded thermoplastic face mask was applied to ensure that the subject’s head remained in a constant position during the scanning period. The exact position of the patient’s head relative to the scanning plane was recorded on a lateral skull film to ensure that the subject’s head remained in a constant position during the scanning period. The exact position of the patient’s head relative to the scanning plane was recorded on a lateral skull film to ensure that the subject’s head remained in a constant position during the scanning period.

Two initial and 7 follow-up studies were performed on the ECAT EXACT HR scanner. A transmission scan was performed before quantitative CMRGlc was determined individually for each of the 14 middle cerebral artery regions in each subject. Mean hemispheric values were calculated. We calculated CMRGlac = CwbLC \[ k_{13} \times k_{23} \times k_3 \], where Cwb is the glucose concentration in whole blood, LC is the lumped constant, and k1, k2, and k3 are rate constants.28 Because of the need to directly compare regional CMRO2 and CMRGlc, the metabolic processing of CMRO2 images for these 5 patients was repeated with regional data from 4.9-mm resolution images. For the purpose of this study, we defined the lumped constant as the value that yielded a mean hemispheric CMRO2/CMRGlc ratio equal to 5.54 in the 7 normal subjects.29 The value for the lumped constant defined in this way was 0.48. A range of normal hemispheric values and ratios of CMRGlc and CMRO2/CMRGlc index was generated from the volunteers. All 5 patients and 7 normal volunteers who had combined CMRO2 and CMRGlc studies were studied on the 961 scanner. These 7 normal volunteers underwent visual stimulation during all scans of the scanning
Results

Normal Subjects

The ranges of left/right and right/left hemispheric ratios in 18 normal volunteers were as follows: CBF ratio = 0.897 to 1.103; CBV ratio = 0.789 to 1.211; CMRO₂ ratio = 0.918 to 1.082; and OEF ratio = 0.918 to 1.082. The normal range for CBF in the middle cerebral artery territory was 35.7 to 78.1 mL/100 g/min. The normal range for CBV was 3.45 mL/100 g/min. The normal range for CMRO₂ was 2.37 to 4.14 mL/100 g/min. The normal range for CMRGluc was 19.64 to 41.69 μmol/100 g/min, and that for CMRO₂/CMRGluc index was 3.89 to 8.99.

Patients

The 10 patients ranged in age from 50 to 79 years of age (mean age, 66.0 years) (Table 1). Seven had symptoms of ischemia in the territory of the occluded carotid artery before study entry (cerebral infarction in 5, transient ischemic attack in 1, and amaurosis fugax in 1). The diagnosis of common or internal carotid artery occlusion was made on selective digital subtraction arteriography in 9 patients and on digital venous angiography in 1. Follow-up PET examinations were obtained 12 to 59 months after initial enrollment. No interval ischemic events were observed or reported between PET examinations. No new deficits were identified on examination. Nine of the 10 patients were receiving antiplatelet or antithrombotic medication (aspirin in 5, ticlopidine in 2, and warfarin sodium in 2) at the time of both the initial and the follow-up PET examinations. Two patients were on 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (lovastatin), both initially and at follow-up (patients 3 and 6 in Table 1). Six patients were on antihypertensive agents, both initially and at follow-up.

No change in mean systolic and diastolic blood pressure (measured before the PET scan) was identified between initial and follow-up examinations. The initial mean ± SD blood pressure was 165 ± 26/89 ± 14 mm Hg (systolic/diastolic), and the follow-up mean pressure was 153 ± 15/85 ± 9 mm Hg (P = 0.14 and P = 0.41, for systolic and diastolic pressure, respectively). Mean arterial oxygen content (± 95% confidence limits) was 0.165 (± 0.014) initially and 0.159 (± 0.016) on follow-up (P = 0.34). Mean arterial carbon dioxide tension was 37.6 mm Hg (± 1.4) initially and 37.3 mm Hg (± 1.3) on follow-up (P = 0.77).

<table>
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<tr>
<th>Pt.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Prior Symptoms</th>
<th>Days From 1st Sx to 1st PET</th>
<th>Days From Last Sx to 1st PET</th>
<th>Angiographic Collaterals</th>
<th>CT/MR Findings</th>
<th>Interval Change in OEF Ratio</th>
<th>Change Between PET, mo</th>
<th>Time Between PET, mo</th>
<th>Glucose Study</th>
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<td>−54</td>
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<td>73</td>
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<td>66</td>
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<td>AF</td>
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Pl indicates patient; Sx, symptoms; TIA, transient ischemic attack; AF, amaurosis fugax; ACoA, anterior communicating artery; OA, ophthalmic artery; Bz, border zone shift; and other ECA, external to internal carotid artery collateral other than OA.
values remained similar between initial and follow-up studies.

CMRGlc was significantly lower in the hemisphere ipsilateral to the occluded carotid artery compared with normal values (t test, $P < 0.001$) but not compared with the contralateral hemisphere (paired t test, $P = 0.219$). However, the ratio of $CMRO_2$ to CMRGlc in the hemisphere ipsilateral to the occluded carotid artery was not different from either normal values or the contralateral side (Table 3).

**Discussion**

The present data demonstrate (1) that abnormally elevated OEF can improve over time in selected patients with carotid artery occlusion and no interval stroke and (2) that improvement in blood flow accounts for the reduction in OEF. We found no evidence of changes in cerebral metabolism in association with improvement in OEF.

Different PET scanners were used in this study. Most of the initial examinations were performed on the ECAT 953B scanner, and most of the follow-up studies were performed on the ECAT EXACT HR (Siemens). It is unlikely that the improvement in OEF and CBF ratios is due to this factor. The scanners have very similar sensitivity, as well as axial and transverse resolution. The use of hemispheric ratios rather than absolute values to identify changes in hemodynamic and metabolic status further reduces the possible impact of any bias due to different scanners.

The results of this study mirror the results of studies of surgical revascularization in patients with carotid occlusion and severe hemodynamic compromise. Powers and coworkers reported PET measurements of CBF, CBV, OEF, and $CMRO_2$ before and after extracranial to intracranial arterial bypass in 6 patients with misery perfusion. A significant improvement in hemispheric ratios of CBF and OEF was found, while CBV and $CMRO_2$ values remained unchanged.

**Figure 1.** A statistically significant improvement in ipsilateral to contralateral CBF and OEF ratios occurred between initial and follow-up PET examinations. CBV and $CMRO_2$ ratios remained unchanged.
Samson and colleagues\(^{30}\) studied 12 patients before and after extracranial to intracranial bypass. Similar results were found in the 2 patients with markedly asymmetrical increased OEF and decreased CBF. Postoperatively, the OEF and CBF ratios improved, while the CMRO\(_{2}\) ratio remained essentially unchanged. Gibbs and coworkers\(^{31}\) reported the effects of extracranial to intracranial bypass on 12 patients. Postoperative measurements of OEF improved in the 4 patients with preoperatively elevated values. In 2 of the 4 patients this was due to interval infarction and reduced CMRO\(_{2}\), however. This evidence provides further support to the conclusion that the increase in collateral flow.

It is important to note that the patients in this study were highly selected by both clinical and imaging criteria. Most importantly, they represent a group with increased OEF who did not experience an ipsilateral ischemic stroke during follow-up. Whether the improvement in OEF and CBF observed in these patients can take place in all patients with carotid occlusion is not known. Patients with increased OEF who do develop ischemic stroke may represent a group not able to improve their collateral sources of flow.

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**TABLE 3. CMRO\(_{2}/\text{CMRGlc}\) Index**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Ipsilateral</th>
<th>Contralateral</th>
<th>Ipsilateral</th>
<th>Contralateral</th>
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<td>22.69</td>
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<td>4.81</td>
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<td>22.65</td>
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<td>25.83</td>
<td>6.38</td>
<td>7.76</td>
</tr>
<tr>
<td>10</td>
<td>25.81</td>
<td>25.83</td>
<td>7.30</td>
<td>5.50</td>
</tr>
</tbody>
</table>

Mean ± SD: 25.29 ± 2.8, 28.22 ± 7.1, 5.63 ± 1.34, 5.93 ± 1.15

Normal mean: 33.37 ± 6.17, 5.54 ± 1.30

*Expressed in micromoles per 100 g per minute.

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**Figure 3.** The longer the time between initial and follow-up PET examination, the larger is the improvement in the OEF ratio. The interval change in the OEF ratio (follow-up minus initial) on the y-axis compared with the length of time (in months) between initial and follow-up OEF measurements is shown.

**Acknowledgments**

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**References**


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