Compensatory Mechanisms for Chronic Cerebral Hypoperfusion in Patients With Carotid Occlusion

Colin P. Derdeyn, MD; Tom O. Videen, PhD; Susanne M. Fritsch, RN; David A. Carpenter, MD; Robert L. Grubb, Jr, MD; William J. Powers, MD

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 r 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

The hemodynamic effect of carotid occlusive disease on the cerebral circulation can be assessed by modern neuroimaging techniques. Even with severe stenosis or occlusion, the distal perfusion pressure and cerebral blood flow (CBF) may remain normal if collateral circulatory pathways are adequate.¹⁻⁴ If perfusion pressure is reduced distal to an occlusive lesion because of inadequate collaterals, CBF can be maintained at normal levels by autoregulatory dilation of resistance vessels. This autoregulatory vasodilation may be identifiable as a reduced or absent CBF response to vasodilatory stimuli such as hypercapnia or acetazolamide.¹ When the capacity for autoregulatory vasodilation to maintain normal blood flow is exceeded, CBF falls relative to cerebral rate of oxygen metabolism (CMRO₂), and oxygen extraction fraction (OEF) increases to maintain normal CMRO₂. This most severe stage of hemodynamic impairment has been termed stage II hemodynamic failure or “misery perfusion.”³ While increased OEF has been shown to be a powerful independent risk factor for subsequent ischemic stroke in patients with symptomatic carotid occlusion, the majority of such patients still remain stroke free.⁶

Previous investigators have reported improvement in cerebral hemodynamic compromise over time. De Ley and coworkers⁷ found a progressive improvement in CO₂ reactivity over the course of 1 month after unilateral carotid artery occlusion in rats. Widder and coworkers⁸ used transcranial Doppler sonography with CO₂ challenge to study 98 patients with carotid occlusion at least twice. They found that CO₂ reactivity improved in more than half of their patients with unilateral carotid occlusion (28 of 55 patients) with diminished or exhausted cerebrovascular reserve. These changes generally occurred within the first few months. Hasegawa and colleagues⁹ reported improvement in vasoreactivity in 3 of 20 patients studied with single-photon emission CT using ¹²³I-idoamphetamine and an acetazolamide challenge.

There are several potential mechanisms by which the brain and cerebral vasculature could adapt to a chronic reduction in CBF relative to CMRO₂ in the absence of cerebral infarction. CBF may increase over time as collateral pathways develop.¹⁰¹¹ Conversely, CMRO₂ may decrease and thus reestablish the balance between CBF and CMRO₂. Sette and colleagues¹² have proposed that downregulation of CMRO₂, which is hemodynamically mediated and possibly reversible, occurs in response to misery perfusion. Selective ischemic neuronal loss in the absence of infarction of all cellular elements has been postulated as a cause of reduced CMRO₂ in regions of brain that are structurally normal.¹³⁻¹⁵ In experimental animals, chronic hypoxia increases cerebral glucose...
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 (2) no interval 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), CMRO₂, 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 obtained after head immobilization. Venous and arterial catheters were placed for intravenous radiotracer administration and for arterial blood gas analyses and arterial time-activity curve determination, respectively.18

PET studies were performed on 1 of 2 scanners (ECAT 953B and ECAT EXACT HR, Siemens) with similar sensitivity and axial and transverse resolution.19,20 All studies were acquired in the 2-dimensional mode with interstice septa extended. Eight initial and 3 follow-up studies were performed on the ECAT 953B scanner. Two initial and 7 follow-up studies were performed on the ECAT EXACT HR scanner. A transmission scan was performed before radiotracer administration with the use of ⁶⁷Ge/⁶⁸Ga rotating rod sources, and images were reconstructed with measured attenuation and scatter correction. The skull film and attenuation data from this scan were used to define the limits of the calvaria for quantitative processing of PET data.21

Each PET study consisted of 3 separate physiological studies. During each, arterial blood samples were drawn by hand or automatically to convert quantitative regional radioactivity data to quantitative physiological measurements. Additional arterial samples were drawn at intervals during the examination for determination of PaCO₂ and arterial oxygen content calculations. CBF was measured with a bolus intravenous injection of ¹⁵O-labeled water.18,22 CBV was measured by inhalation of air containing trace amounts of carbon monoxide labeled with ¹⁵O.23 OEF was measured after 1 or 2 breaths of ¹⁵O-labeled oxygen in combination with data from the CBV and CBF measurements.24 CMRO₂ was calculated on a pixel-by-pixel basis as the product of OEF, CBF, and arterial oxygen content.25

After the measurement of CBV, CBF, and OEF, studies of glucose metabolism using ¹⁸F-labeled 2-deoxy-2-fluoro-D-glucose (¹⁸FDG) were performed in 5 patients and 7 normal volunteers. Ten milliequivalents of ¹⁸FDG was injected intravenously.25 Dynamic data acquisition was begun at the time of injection for 96 minutes according to the following schedule: sixteen 30-second frames, eight 1-minute frames, sixteen 2-minute frames, and sixteen 3-minute frames. Arterial samples were obtained at frequent intervals during a 96-minute dynamic scan.

Data Analysis

For all initial and follow-up examinations, PET images were reconstructed with a ramp filter cutoff at the Nyquist frequency to produce images with resolutions of 4.3 mm (953B) or 4.9 mm (EXACT HR) full width at half maximum. These images were then smoothed to a uniform resolution of 16 mm full width at half maximum with the use of a 3-dimensional gaussian filter. All PET data were converted to uniform atlas space to allow reproducible placement of regions of interest.21 For each patient and normal volunteer, 7 spherical regions of interest 19 mm in diameter were placed in the cortical territory of the middle cerebral artery in each hemisphere with the use of stereotaxic coordinates.26 Areas of prior infarction identified on CT or MR images, as well as corresponding contralateral regions, were excluded from analysis. The mean hemispheric values of CBF, CBV, CMRO₂, and OEF were then calculated.

In the first group of normal control subjects, the ratios of the left to right and right to left hemispheric mean OEF were calculated to establish a normal range for OEF ratios. Normal ranges for the ratios of CBF, CBV, and CMRO₂ were also calculated. Ipsilateral to contralateral (relative to the side of occlusion) ratios of the mean hemispheric OEF were calculated for all patients. Changes in the OEF ratio over time were assessed by comparing the initial and follow-up mean ratios (paired t test, P<0.05). The magnitude of the change in OEF as a function of time was investigated with the use of linear regression analysis (P<0.05). In addition, changes in CBF, CBV, and CMRO₂ were analyzed (P<0.05). Changes in absolute mean hemispheric values of OEF, CBF, CBV, and CMRO₂ were similarly analyzed.

Dynamic ¹⁸FDG scans were reconstructed with a ramp filter cutoff at the Nyquist frequency to produce images with resolutions of 4.9 mm full width at half maximum. Dynamic PET data and arterial whole blood time-activity curves were processed with a modified Marquardt parameter estimation routine and a model with 4 rate constants and a term for blood volume, similar to the approach used by Fiorelli and coworkers.27 Quantitative CMRGlc was determined individually for each of the 14 middle cerebral artery regions in each subject. Mean hemispheric values were calculated. We calculated CMRGlc=Cwb/LC [k1/k2+k3]), 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
session. All changes in CBF induced by the visual stimulus were remote from the middle cerebral artery regions used for this analysis.

### 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; CMRO$_2$ 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$^{-1}$·min$^{-1}$. The normal range for CBV was 1.91 to 3.45 mL·100 g$^{-1}$. The normal range for CMRO$_2$ was 2.37 to 4.14 mL·100 g$^{-1}$·min$^{-1}$. The normal range for CMRGlc was 19.64 to 41.69 μmol·100 g$^{-1}$·min$^{-1}$, and that for CMRO$_2$/CMRGlc 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 angiography in 9 patients and on digital venous angiography in 1. Follow-up PET examinations were obtained 12 to 59 months after initial enrollment. Clinical examinations were repeated at the time of the follow-up PET studies. 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 ($P = 0.77$).

### Hemodynamic and Metabolic Measurements

The ranges of CBF, CBV, CMRO$_2$, and OEF values measured at baseline in the middle cerebral regions ipsilateral to the carotid occlusion in the 10 patients were 29.5 to 68.7 mL·100 g$^{-1}$·min$^{-1}$, 1.99 to 4.92 mL·100 g$^{-1}$, 1.79 to 5.42 mL·100 g$^{-1}$·min$^{-1}$, and 0.27 to 0.86, respectively. Contralateral values of CBF, CBV, CMRO$_2$, and OEF ranged from 36.3 to 83.6 mL·100 g$^{-1}$·min$^{-1}$, 1.73 to 4.74 mL·100 g$^{-1}$, 1.90 to 5.35 mL·100 g$^{-1}$·min$^{-1}$, and 0.25 to 0.704, respectively. Follow-up values of ipsilateral CBF, CBV, CMRO$_2$, and OEF ranged from 34.1 to 59.1 mL·100 g$^{-1}$·min$^{-1}$, 2.89 to 6.5 mL·100 g$^{-1}$, 2.03 to 3.60 mL·100 g$^{-1}$·min$^{-1}$, and 0.28 to 0.55, respectively. Follow-up contralateral values of CBF, CBV, CMRO$_2$, and OEF ranged from 32.6 to 74.0 mL·100 g$^{-1}$·min$^{-1}$, 2.24 to 5.46 mL·100 g$^{-1}$, 2.30 to 3.71 mL·100 g$^{-1}$·min$^{-1}$, and 0.29 to 0.54, respectively.

The initial mean ipsilateral to contralateral OEF for the 10 patients was 1.164 (Table 2). This mean ratio fell to 1.076 on follow-up ($P = 0.022$). Absolute OEF in the ipsilateral hemisphere fell from a mean of 0.478 to 0.411 ($P = 0.177$, not significant). Individually, the OEF ratio fell in 8 patients and rose slightly in 2 (Figure 1). The follow-up OEF ratio was within the normal range in 5 of the 8 patients (Figures 1 and 2). The improvement in the OEF ratio was a function of time (Figure 3).

Examination of other variables revealed a parallel increase in the mean ratio of ipsilateral to contralateral CBF from 0.806 to 0.847 ($P = 0.021$) (Table 2). An increase in the ipsilateral mean CBF was observed but did not reach statistical significance (40.8 to 47.8 mL·100 g$^{-1}$·min$^{-1}$; $P = 0.056$). CBV and CMRO$_2$ ratios and mean hemispheric
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 CMRO2 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 CMRO2 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 CMRO2 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 CMRO2 ratios remained unchanged.

**Figure 2.** Interval improvement in OEF in a 72-year-old woman with left carotid occlusion (patient 5 from Table 1). The initial PET examination (top row) shows reduced blood flow (CBF, left image) and reduced CMRO2 (middle image) corresponding to a left capsular and frontal infarction (left hemisphere is on the left of the PET images by laboratory convention). OEF (right image) is elevated throughout the left MCA territory. Follow-up PET examination 39 months later (bottom row) shows normalization of the OEF abnormality (bottom right image). Note the change in the scale for the CBF and CMRO2 images, which demonstrates an increase in absolute values of flow and metabolism over time.

### Table 2. Initial and Follow-Up Mean Hemispheric Values and Ratios for 10 Patients With Increased Baseline OEF

<table>
<thead>
<tr>
<th>PET</th>
<th>CBF, mL/(100 g · min)</th>
<th>CBV, mL/100 g</th>
<th>CMRO2, mL/(100 g · min)</th>
<th>OEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>40.8±11.5</td>
<td>3.29±0.96</td>
<td>3.15±1.30</td>
<td>0.478±0.170</td>
</tr>
<tr>
<td>Contralateral</td>
<td>50.8±13.3</td>
<td>3.33±0.93</td>
<td>3.33±1.16</td>
<td>0.408±0.134</td>
</tr>
<tr>
<td>Ratio</td>
<td>0.806±0.107</td>
<td>0.997±0.159</td>
<td>0.932±0.099</td>
<td>1.164±0.062</td>
</tr>
<tr>
<td>Repeated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>47.8±8.4</td>
<td>3.56±1.15</td>
<td>2.95±0.53</td>
<td>0.411±0.073</td>
</tr>
<tr>
<td>Contralateral</td>
<td>57.0±14.0</td>
<td>3.38±1.00</td>
<td>3.23±0.40</td>
<td>0.387±0.071</td>
</tr>
<tr>
<td>Ratio</td>
<td>0.847±0.122</td>
<td>1.046±0.120</td>
<td>0.904±0.121</td>
<td>1.076±0.074</td>
</tr>
<tr>
<td>Values are mean±SD.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Samson and colleagues 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 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 improvement observed in this study can be attributed to increases 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.

**Table 3. CMRO$_2$/CMRGlc Index**

<table>
<thead>
<tr>
<th></th>
<th>CMRGlc*</th>
<th>CMRO$_2$/CMRGlc</th>
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<tbody>
<tr>
<td></td>
<td>Ipsilateral</td>
<td>Contralateral</td>
</tr>
<tr>
<td>Pt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22.69</td>
<td>23.18</td>
</tr>
<tr>
<td>5</td>
<td>29.49</td>
<td>40.23</td>
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<td>6</td>
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<tr>
<td>9</td>
<td>25.79</td>
<td>25.83</td>
</tr>
<tr>
<td>10</td>
<td>25.81</td>
<td>25.83</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>25.29±2.8</td>
<td>28.22±7.1</td>
</tr>
<tr>
<td>Normal mean</td>
<td>33.37±6.17</td>
<td></td>
</tr>
</tbody>
</table>

*Expressed in micromoles per 100 g per minute.

**References**


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