Cerebral Perfusion Reserve Indexes Determined by Fluoromethane Positron Emission Scanning

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An index of cerebral perfusion reserve (RES%), defined as the percent change of regional cerebral blood flow over baseline per mm Hg of end-tidal CO₂ tension, was determined for each middle cerebral artery (MCA) territory in patients with unilateral carotid distribution transient ischemic attacks or minor cerebrovascular accidents and was compared with that of age-matched, neurologically normal volunteers. Vasodilator responses to induced hypercapnia were tested during inhalation of 5% CO₂ in 95% O₂ while regional cerebral blood flow was measured by fluoromethane inhalation positron emission tomography. Mean RES% for 24 normal MCA territories was 5.2±0.8%. Mean RES% for 15 patient nonischemic MCA territories was 3.8±1.3% and for 15 ischemic MCA territories was 2.8±1.9% (both p<0.001). Individual RES% values and symmetry ratios between ischemic and nonischemic regions were also determined and compared with angiographic data. Areas of diminished, asymmetric, or paradoxical (two patients) CO₂ reactivity appear to correspond to areas of compensatory vasodilation. We found this technique to be a safe and reproducible method for defining and recording localized areas of cerebral tissue at apparent risk for hemodynamically related damage.

(Stroke 1988;19:19–27)

The measurement of cerebral perfusion reserve may provide an objective method to identify patients at risk for infarction due to hemodynamic failure. Progressive atherosclerosis in the major cerebral arteries may alter perfusion to the respective peripheral arterial vascular beds. A number of studies have demonstrated that measurements during induced hypercapnia uncover areas of regional vascular compromise where none are apparent otherwise. It is also possible that delayed ischemia results from the reduced capacity of the cerebral circulation to adapt to physiologic variations in blood gases. Since the cerebral vasculature is provided with several potential collateral pathways, adequacy of these collateral pathways predicted by the ability to increase regional cerebral blood flow (rCBF) in response to induced hypercapnia should help determine eventual clinical outcome. In this study, dynamics of the rCBF and vasodilator response to induced hypercapnia were investigated using noninvasive fluorine-18-fluoromethane (¹⁸FCH₃) inhalation positron emission tomography (PET) in patients with unilateral internal carotid artery (ICA) distribution transient ischemic attacks (TIAs) or minor cerebrovascular accidents (CVAs) and were compared with responses measured in normal volunteers.

An index of cerebral perfusion reserve (RES%), defined as the percent change of regional cerebral blood flow over baseline per mm Hg of end-tidal CO₂ tension, was determined for each middle cerebral artery (MCA) territory in patients with unilateral carotid distribution transient ischemic attacks or minor cerebrovascular accidents and was compared with that of age-matched, neurologically normal volunteers. Vasodilator responses to induced hypercapnia were tested during inhalation of 5% CO₂ in 95% O₂ while regional cerebral blood flow was measured by fluoromethane inhalation positron emission tomography. Mean RES% for 24 normal MCA territories was 5.2±0.8%. Mean RES% for 15 patient nonischemic MCA territories was 3.8±1.3% and for 15 ischemic MCA territories was 2.8±1.9% (both p<0.001). Individual RES% values and symmetry ratios between ischemic and nonischemic regions were also determined and compared with angiographic data. Areas of diminished, asymmetric, or paradoxical (two patients) CO₂ reactivity appear to correspond to areas of compensatory vasodilation. We found this technique to be a safe and reproducible method for defining and recording localized areas of cerebral tissue at apparent risk for hemodynamically related damage.

(Stroke 1988;19:19–27)

Subjects and Methods

rCBF was studied using the ¹⁸FCH₃ inhalation method and an Ortec ECAT-II positron scanner (Oak Ridge, Tennessee). Spatial resolution for the PET images was 16 mm in the plane of section; slice thickness was 18 mm. Scans were obtained at a single plane of study 4 cm above and parallel to the orbital meatal line and were compared with standard anatomic and computed tomographic (CT) atlases to identify neuroanatomic structures. Measured attenuation images were obtained using a germanium ring source at the plane of study. End-tidal carbon dioxide tension (Peco₂) was registered during each rCBF study using a Beckman gas analyzer (Fullerton, California). Inhalation of 25–40 mCi ¹⁸FCH₃ was followed by 2 minutes of normocapnic rebreathing from a dry spirometer with a soda lime CO₂ trap in the rebreathing loop to ensure that the CO₂ concentration in the inhaled gas remained normal. Rebreathing was followed by a long washout period. A dynamic sequence of 12 1-minute scans was initiated at inhalation, which, with the measured expired-breath activity curve, constitutes input data to derive the best-fit rCBF and blood–brain partition coefficient. End-tidal expired gas measurements were used to describe the temporal behavior of the arterial blood concentration, whereas venous blood samples provided the absolute scaling. The rapid biologic clearance of ¹⁸FCH₃ allowed serial examinations at 20-minute intervals with <5% of the activity administered persisting at that time. Thus, data were collected a second time after inhalation of 25–40 mCi ¹⁸FCH₃, followed by rebreathing 5% CO₂ in 95% O₂; this represented the induced hypercapnic rCBF data. Each patient was primed for the hypercapnic study by breathing 5% CO₂ for 3–4 minutes before ¹⁸FCH₃-plus 5% CO₂ inhalation. All paired studies were performed.
in normocapnic–hypercapnic order. We had previously validated these techniques with invasive blood sampling. 6

rCBF data were expressed as milliliters per 100 grams per minute. For quantitative analysis of the PET images, fixed whole slice, symmetric right and left hemispheric, and symmetric middle cerebral artery (MCA) territories were drawn only once as a template for analysis across all studies. The whole MCA region was chosen as it was believed to be a truer representation of ICA flow than hemispheric data. We did not seek to identify ischemic foci in this study. Average rCBF for each territory in the planar images was determined as blood flow counts per pixel in a 128 × 128 pixel grid. Percent change of rCBF over room air (RA) baseline per mm Hg Pco2 for each territory, index of cerebral perfusion reserve (RES%) as used by Olsen et al, 7 was expressed as:

\[
RES% = \left[ \frac{rCBF_{CO2} - rCBF_{RA}}{rCBF_{RA}} \right] \times 100
\]

In addition, left:right (L/R) and ischemic:nonischemic RES% symmetry ratios were determined for MCA territories in normal volunteers and patients, respectively.

Control 95% and 99% confidence intervals (CIs) were determined for mean RES% and mean L/R symmetry ratio in the normal volunteers. Control 99% CIs

### Table 1. Clinical and Radiographic Features in Patients With Carotid Distribution Transient Ischemic Attacks or Minor Stroke

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<th>Pt</th>
<th>CT</th>
<th>Type of angiogram</th>
<th>Days PET to CT</th>
<th>Angio</th>
<th>% Sten</th>
<th>Source of flow</th>
<th>L ECA</th>
<th>% Sten</th>
<th>Reversal</th>
<th>% Sten</th>
<th>Source of flow</th>
<th>R ECA</th>
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Pt, patient; CT, computed tomography; PET, position emission tomography; L, left; ICA, internal carotid artery; ECA, external carotid artery; R, right; % Sten, percent stenosis; MCA, middle cerebral artery; ACA, anterior cerebral artery; nl, normal; TIAs, transient ischemic attacks; IVDSA, intravenous digital subtraction angiography; nd, not determined; PCA, posterior cerebral artery; OD, right eye; OS, left eye; CVA, cerebrovascular accident; RIND, reversible ischemic neurologic deficit. Status as defined in "Subjects and Methods."
Table 1. (continued)

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<td>Minor L. MCA CVA 40 days prior, Status II</td>
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are one of the normative standards against which all patient data were plotted. In this way, we illustrated individual patient variation from the normal ranges and tried to show how particular patient subgroups fared relative to the normal ranges. Because the data were not normally distributed, the Wilcoxon two-sample rank test was used to compare normal and patient groups and the Wilcoxon signed rank test was used to compare ischemic and nonischemic cortexes with each patient serving as his own control. Informed consent was obtained from all subjects.

Patients. In all patients the diagnosis of unilateral ICA distribution TIA or minor CVA was based on history, clinical examination, and plain CT scan of the brain (Table 1); only those with an ischemic event confined to the territory of one ICA are included in this report. All patients underwent angiography (10 selective arterial, five intravenous digital subtraction [IVDSA]) within a mean ± SD of 3.7 ± 3.4 (range 1-12) days of PET study. All patients also underwent plain CT within 3.5 ± 2.2 (range 1-7) days of rCBF study. The clinical condition of the patients examined was Status 0 (9 with either amaurosis fugax or hemispheric TIA, 1 with hemispheric reversible ischemic neurologic deficit [RIND]), Status I (1 with minor hemispheric CVA and no impairment), or Status II (4 with minor hemispheric CVA and mild impairment) assigned according to the classification system of the Ad Hoc Committee on Cerebrovascular Diseases. All patients were being considered for surgery. Although arterial blood pressure was not recorded during the rCBF studies, no patient had clinically documented hypotension.

Normal volunteers. The volunteers were all neurologically normal and devoid of cerebrovascular risk factors. Normal volunteers did not undergo angiography, CT scanning, or carotid Doppler examination.

Results

rCBF for normal volunteers and patients are presented in Tables 2 and 3, respectively. Table 4 compares the means and CIs for variables in the two groups. Individual values for the patients that fall outside the CIs are labeled in Table 3. Figure 1 illustrates the individual RES% data points for normal volunteers and patients with the rCBF for each group mean and distribution related using the Wilcoxon two-sample rank test. The Wilcoxon signed rank test fails to show a significant difference between actual ischemic and nonischemic RES% values.

Age, Peco₂ range, and Peco₂ are not significantly different between the normal and patient groups. RA and hypercapnic rCBF are significantly (p<0.005) lower for patients than for normal volunteers (Table 4). RES% and L/R ratios for control nonischemic cortexes serve as the standard of comparison throughout this report; patients' ischemic cortexes are compared with their respective nonischemic cortexes in displaying side-to-side asymmetry (Figure 2).

Middle Cerebral Artery Data

Cerebral perfusion reserve; nonischemic cortex. The mean value for absolute MCA territory vasodilator responsiveness for the normal volunteers was 5.2 ± 0.8%, with 99% CIs of 2.8-7.6%. Mean RES% for the patients' nonischemic cortexes was 3.8 ± 1.3% (p<0.001). Patients 1-8 and 10 had normal RES% values (range 3.8-5.8%) in their respective nonischemic MCA territories (Tables 3 and 5). Although the asymptomatic ICAs for Patients 5, 6, 8, and 10 were all at least 50% stenosed (Table 5), RES% was normal.

Cerebral perfusion reserve; ischemic cortex. The mean value for vasodilator responsiveness for the patients' ischemic cortexes was 2.8 ± 1.9% (p<0.001). Patients 1-6 and 9 had normal RES% values in their respective symptomatic MCA territories (Tables 3 and 6). Although the symptomatic ICAs were narrowed at 70% and >70% for Patients 5 and 9, respectively, RES% remained normal (Table 6). Patients 7, 8, and 10-15 had RES% values (range -0.1 to 2.6%) outside the 99% CI (Tables 3 and 6). Patients 7, 11, and 12 had...
Table 2. Cerebral Blood Flow and Cerebral Perfusion Reserve Indexes for Neurologically Normal Volunteers Without Risk Factors for Stroke

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Δ Pco2</th>
<th>rCBF_H</th>
<th>rCBF_MCA</th>
<th>rCBF_H</th>
<th>rCBF_MCA</th>
<th>Left/Right symmetry of RES%</th>
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Δ Pco2, difference in expired Pco2 between room air and hypercapnic states; rCBF, regional cerebral blood flow; H, cerebral hemisphere; MCA, middle cerebral artery; RES%, percent change in rCBF per mm Pco2; RA, room air; CO2, hypercapnia.

Table 3. Cerebral Blood Flow and Cerebral Perfusion Reserve Indexes for Patients With Carotid Distribution Transient Ischemic Attacks or Minor Strokes

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age (years)</th>
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<th>rCBF_MCA</th>
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<td>11</td>
<td>65</td>
<td>16.8</td>
<td>38</td>
<td>51</td>
<td>1.9†</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>67</td>
<td>19.6</td>
<td>26</td>
<td>37</td>
<td>2.2†</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>68</td>
<td>12.6</td>
<td>25</td>
<td>29</td>
<td>1.5†</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>14</td>
<td>64</td>
<td>10.2</td>
<td>37</td>
<td>43</td>
<td>1.6†</td>
<td>33</td>
<td>30 (−0.1)†</td>
</tr>
<tr>
<td>15</td>
<td>71</td>
<td>9.9</td>
<td>26</td>
<td>28</td>
<td>0.7†</td>
<td>25</td>
<td>23 (−0.1)†</td>
</tr>
</tbody>
</table>

Δ Pco2, difference in expired Pco2 between room air and hypercapnic states; rCBF, regional cerebral blood flow; H, cerebral hemisphere; MCA, middle cerebral artery; RES%, percent change in rCBF per mm Pco2; RA, room air; CO2, hypercapnia.

*Values outside 95% confidence interval (CI) and Z ranking of ±2; †values outside 95% CI and Z ranking of ±3; ‡values outside Z ranking of ±2.
Table 4. Data (mean±SD) for Normal Volunteers and Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal volunteers</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonischemic cortex</td>
<td>Nonischemic cortex</td>
</tr>
<tr>
<td>No. of hemispheres</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>Age years</td>
<td>54±20</td>
<td>63±8</td>
</tr>
<tr>
<td>Room air variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rCBF ml/100 g/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemispheric</td>
<td>41±4.0</td>
<td>33±7.3*</td>
</tr>
<tr>
<td>MCA</td>
<td>41±4.4</td>
<td>32±11.7*</td>
</tr>
<tr>
<td>PecO₂ mm Hg</td>
<td>34.2±3.7</td>
<td>32.6±5.6</td>
</tr>
<tr>
<td>Hypercapnic variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rCBF ml/100 g/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemispheric</td>
<td>66±8.0</td>
<td>49±11.7*</td>
</tr>
<tr>
<td>MCA</td>
<td>66±7.5</td>
<td>50±12.7*</td>
</tr>
<tr>
<td>PecO₂ mm Hg</td>
<td>45.6±3.9</td>
<td>46.0±6.2</td>
</tr>
<tr>
<td>Δ PecO₂ mm Hg</td>
<td>11.3±2.8</td>
<td>12.8±3.6</td>
</tr>
<tr>
<td>RES%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemispheric</td>
<td>5.4±0.7</td>
<td>4.0±1.1†</td>
</tr>
<tr>
<td>95% CI range</td>
<td>4.0–6.8</td>
<td></td>
</tr>
<tr>
<td>99% CI range</td>
<td>3.3–7.5</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>5.2±0.8</td>
<td>3.7±1.3†</td>
</tr>
<tr>
<td>95% CI range</td>
<td>3.6–6.8</td>
<td></td>
</tr>
<tr>
<td>99% CI range</td>
<td>2.8–7.6</td>
<td></td>
</tr>
<tr>
<td>Symmetry ratios</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemispheric</td>
<td>1.0±0.06</td>
<td>0.83±0.20‡</td>
</tr>
<tr>
<td>95% CI range</td>
<td>0.88–1.12</td>
<td></td>
</tr>
<tr>
<td>99% CI range</td>
<td>0.82–1.18</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>1.0±0.08</td>
<td>0.68±0.43§</td>
</tr>
<tr>
<td>95% CI range</td>
<td>0.85–1.16</td>
<td></td>
</tr>
<tr>
<td>99% CI range</td>
<td>0.76–1.24</td>
<td></td>
</tr>
</tbody>
</table>

rCBF, regional cerebral blood flow; MCA, middle cerebral artery region of interest; RES%, percent change in rCBF per mm PecO₂; CI, confidence interval.

*p<0.005; †p<0.001; ‡p<0.002; §p<0.02 by Wilcoxon two-sample rank testing.

Discussion
Methodologic Considerations

The ¹⁸FCH₃ PET method for measuring rCBF provides blood flow maps in the axial plane that add anatomic specificity to the rCBF data. These local measurements offer the opportunity to view changes within and around areas of cerebral ischemia or infarction. Areas with a diminished ability to increase blood flow during induced hypercapnia are of particular interest since these regions may be at risk for infarction on the basis of hemodynamic fluctuations. It generally has been assumed that the normal increase in rCBF occurring with an increase in CO₂ levels, such as that seen during hypercapnic PET studies, is due to a decrease in cerebrovascular resistance resulting from dilation of cerebral vessels.⁹,¹⁰

We did not invasively monitor Paco₂, nor did we determine rCBF relative to mean arterial blood pressure (MABP). Since cerebral blood vessels are able to dilate to compensate for a fall in arterial blood pressure, it is not expected that in hypotensive states the cerebral vessels, being already maximally dilated, would dilate further in response to increases in CO₂ tension.¹¹ None of the patients included in this report, however, had clinically documented hypotension at rest. In addition, the supine position of the subjects during PET evaluation minimizes orthostasis. Serial blood pressure determinations will, however, be added to our scanning protocol in an attempt to properly relate CO₂ and rCBF with changes in MABP, if any.

Cerebral Vasodilator Responsiveness

The addition of CO₂ to the inhaled ¹⁸FCH₃ mixture is followed by cerebral vasodilation and increased rCBF. There is a functional cerebrovascular reserve or ability of the cerebral vessels to lower their resistance in response to decreases in cerebral perfusion pressure, and a measure of this reserve is the responsiveness of the rCBF to increased CO₂ tension.¹² In our present study, noninvasive measurement of rCBF has made possible the testing of vasodilator responsiveness in a group of 12 normal, healthy volunteers of different ages. The
mean control value for absolute MCA territory vasodilator responsiveness is $5.2 \pm 0.8\%$, in reasonable agreement with values reported with the use of xenon inhalation$^{13,14}$ and invasive intra-arterial xenon techniques.$^{15,16}$ This value is compared with that from a heterogeneous group of 15 symptomatic vascular patients (Table 3) whose mean values for vasodilator responsiveness are $3.7 \pm 1.3\%$ and $2.8 \pm 1.8\%$ for nonischemic and ischemic regions, respectively; these are also in reasonable agreement with previously reported values.$^{13-16}$ The finding of significantly lowered reserve values in the asymptomatic, nonischemic cortices of some of our patients is in keeping with the widespread pathologic nature of atherosclerotic occlusive cerebrovascular disease.$^{14}$

Cerebral infarcts. Abnormalities of CO$_2$ responsiveness is often observed during the acute stroke phase.$^{17}$ Various forms of cerebrovascular disease may significantly affect the usual increase in rCBF that occurs with induced hypercapnia.$^{18}$ Paulson$^{19}$ and Paulson et al$^{20}$ described focal vasoparalysis with loss of vasodilation during hypercapnia in patients with cerebral apoplexy (stroke) regardless of whether angiography showed occlusion of a major vessel. In an experimental MCA occlusion model, Waltz$^{10}$ described the failure of changes in PaCO$_2$ to produce changes in rCBF or in the caliber of arterial vessels in the majority of the ischemic cortices studied within 1 day of occlusion. However, CO$_2$ responsiveness improved significantly when restudied 5–12 days after MCA occlusion.$^{10}$ Tuteur et al,$^{22}$ using a steady-state krypton-85 technique, reported slight decreases in steady-state rCBF responses to CO$_2$ in a very heterogeneous group of patients with cerebrovascular disease. In a group of eight patients with deep subcortical infarcts, Olsen et al$^7$ showed preservation of CO$_2$ responsiveness in all ischemic areas in patterns similar to that of the nonischemic/nonhyperemic areas. Only one of these patients, however, was subjected to induced hypercapnia. Yamamoto et al$^{14}$ described CO$_2$ responsiveness that was markedly impaired in both ischemic and nonischemic hemispheres in the acute stage of patients with cerebral infarction or TIA.

Fluoromethane PET techniques have previously shown more accurate assessments of the specified region of brain dysfunction than plain CTs.$^5$ In our present study, ischemic foci (infarcts in Patients 7, 11, 12, 14, and 15) are even more clearly delineated by determining RES%. Patients 12, 14, and 15 had clearly abnormal CO$_2$ responsiveness that correlated well with their subacute infarct locations and their impaired collateral flow patterns seen on angiography. In spite of old, small, deep infarctions and normal angiography, RES% of Patients 7 and 11 fell well below the normal range. We wonder if this is indicative of multiple small-vessel disease as yet undefined in these patients. The infarcts in Patients 1–3 did not seem to influence blood flow or reserve values. We speculate that this is because of delayed timing and/or otherwise excellent angiographic flow patterns.

It is conceivable that by analyzing smaller regions

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Individual cerebral perfusion reserve index (RES%). Mean middle cerebral artery data ± 95% SEM (vertical error bars) p values compared using Wilcoxon two-sample rank test. Wilcoxon signed rank test fails to show significant difference between groups (*) but matched-pair two-group designs analysis of natural log-transformed data reveals p<0.005. Shaded area represents 99% confidence interval of normal volunteers (controls).}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Individual symmetry ratios. Mean middle cerebral artery ± 95% SEM (vertical error bars) p values compared using Wilcoxon two-sample rank test. Shaded area represents 99% confidence interval of normal volunteers (controls).}
\end{figure}
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Table 5. Cerebral Perfusion Reserve in Nonischemic Cortex of Patients Compared With Angiographic Patterns

<table>
<thead>
<tr>
<th>Primary ICA supply</th>
<th>RES%</th>
<th>Nonstenotic</th>
<th>≥50% stenosis</th>
<th>Occlusion, collateral Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td>Patients 1–8, 10</td>
<td>Patient 5: 50% stenosis on nonischemic, 70% stenosis on ischemic side</td>
<td>None</td>
</tr>
<tr>
<td>Patient 3: contralateral ICA occlusion</td>
<td>Patient 6: &gt;50% stenosis on nonischemic, occlusion on ischemic side</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 4: contralateral ICA occlusion</td>
<td>Patient 8: &gt;70% stenosis on nonischemic side</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diminished</td>
<td></td>
<td>Patients 9, 11–15 (outside 99% CI of controls)</td>
<td>Patient 10: &gt;50% stenosis on nonischemic, 99% on ischemic side</td>
<td></td>
</tr>
<tr>
<td>Patient 11: IVDSA</td>
<td>Patient 9: 90% stenosis on nonischemic, 70% stenosis on ischemic side; incomplete circle</td>
<td>Patient 12: contralateral nonstenotic, Q ? (IVDSA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 13: 80% stenosis on nonischemic, occlusion on ischemic side (IVDSA)</td>
<td>Patient 14: bilateral ICA occlusion, Q ? (IVDSA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 15: &gt;50% stenosis on nonischemic, occlusion on ischemic side; incomplete circle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICA, internal carotid artery; RES%, cerebral perfusion reserve percent; Q, flow; IVDSA, intravenous digital subtraction angiography (all other patients underwent standard angiography); CI, confidence interval.

within the symptomatic MCA territory or infarcted area, we might have shown more abnormal RES% values. We have emphasized the whole MCA territory in this study as that is the area that bears the brunt of ischemia caused by ICA stenosis or occlusion. We have, however, avoided varying the size of our MCA template so as to be able to compare standard areas across normal volunteers and patients.

Transient ischemic attacks. Thompson described preserved responsiveness of rCBF to CO₂ in six TIA patients and believed that this militates against the theory that hemodynamic instability due to fixed obstruction to flow is the basis of TIA. His patients, however, did not undergo angiography. With respect to the responsiveness of rCBF to changes in Paco₂, Tsuda et al. reported preserved reactivity in two

Table 6. Cerebral Perfusion Reserve in Ischemic Cortex of Patients Compared With Angiographic Patterns

<table>
<thead>
<tr>
<th>Primary ICA supply</th>
<th>RES%</th>
<th>Nonstenotic</th>
<th>≥50% stenosis</th>
<th>Occlusion, collateral Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td>Patients 1–6, 9</td>
<td>Patient 5: 70% stenosis on ischemic, 50% on nonischemic side</td>
<td>Patient 3: Q from normal contralateral ICA</td>
</tr>
<tr>
<td>Patient 9: 90% stenosis on nonischemic, 70% stenosis on ischemic side</td>
<td>Patient 4: Q from normal contralateral ICA and PCA</td>
<td>Patient 6: Q from &gt;50% stenosed contralateral ICA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diminished</td>
<td></td>
<td>Patients 7, 8, 10–15 (outside 99% CI of controls)</td>
<td>Patient 10: &gt;90% stenosis on ischemic, &gt;50% on nonischemic side</td>
<td>Patient 8: Q from &gt;70% stenosed contralateral ICA</td>
</tr>
<tr>
<td>Patient 11: IVDSA</td>
<td>Patient 10: 99% stenosis on ischemic, &gt;50% on nonischemic side</td>
<td>Patient 12: IVDSA, contralateral occlusion</td>
<td>Patient 13: contralateral 80% ICA stenosis, Q ? (IVDSA)</td>
<td></td>
</tr>
<tr>
<td>Patient 14: bilateral ICA occlusion, Q ? (IVDSA)</td>
<td>Patient 15: Q from &gt;50% stenosed contralateral ICA and 80% stenosed ipsilateral ICA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICA, internal carotid artery; RES%, cerebral perfusion reserve percent; Q, flow; IVDSA, intravenous digital subtraction angiography (all other patients underwent standard angiography); CI, confidence interval; PCA, posterior cerebral artery; ECA, external carotid artery.
groups of TIA patients due to ICA occlusion and mild ICA stenosis. The mean hemispheric values for absolute vasodilator responsiveness in that study were 3.68 ± 0.36% and 2.93 ± 0.31% for control and ICA occlusion patients, respectively. In our present series, 10 TIA patients (Patients 1, 2, 4–6, 8–11, and 13) were studied. Reserve values were diminished in the nonischemic cortex of 3 patients (Patients 9, 11, and 13) and in the ischemic cortex of 5 patients (Patients 6, 8, 10, 11, and 13). All except 1 of this subgroup (Patient 11) had major ICA stenoses or occlusions bilaterally.

Patients 14 and 15 in this study showed paradoxical CO₂ responsiveness in their symptomatic MCA territories in a fashion similar to that reported previously in the literature. These ischemic areas became maximally vasodilated and were unable to respond to the intense vasodilation promoted by hypercapnia.

**Interhemispheric Symmetry Ratios**

It is well known that the hemodynamic effect of an arterial stenosis or occlusion is rarely predictable. In our present study, only six patients (Patients 1–5 and 11) had RES% symmetry ratios within the 99% CI of normal data. Although Patient 3 had both a subacute
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MCA infarct and an ICA occlusion, his flow values remained normal. If the collateral circulation between the two carotid artery territories is sufficient in a patient with a severe one-sided stenosis or occlusion of a carotid artery, then the blood flow and the vasodilator responsiveness in the two hemispheres will probably be equal or almost equal.

Acknowledgments

We wish to thank Drs. Benjamin Rix Brooks and Martin C. Salinsky for their advice and Ms. Susan Melvin for her clerical assistance.

References

8. Ad Hoc Committee established by the Advisory Council for the National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health: A classification of disorders and patients with cerebrovascular disease; correlations with clinical and angiographic findings. Stroke 1986;17:564–577
12. Melvin for her clerical assistance.
19. Symon L: Experimental evidence for "intracerebral steal" following CO2 inhalation. Scan J Clin Lab Invest 1968;22(S102):13A
25. Symon L: Experimental evidence for "intracerebral steal" following CO2 inhalation. Scan J Clin Lab Invest 1968;22(S102):13A

Key Words • tomography, emission computed • cerebral blood flow • hypercapnia
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