Reduction of regional cerebral blood flow (rCBF) and metabolism in the hemisphere contralateral to unilateral supratentorial infarction is a frequent observation.1-4 This phenomenon has been attributed to transcallosal neuronal disconnection (diaschisis) rather than to bilateral structural cerebrovascular disease.5-11 Recent studies using positron emission tomography (PET), however, have challenged the concept of transhemispheric diaschisis as they found no depression of rCBF in the contralateral hemisphere.6,12,13 Possible reasons for this discrepancy include differences in the selection of controls and uncontrolled influences of other determinants of rCBF.13

All previous series of contralateral flow reduction tacitly assume that they were evaluating strictly unilateral stroke and unilateral vascular disease. These assumptions may have been erroneous. Some authors depend on cranial computed tomography (CT) and others on cerebral angiography to exclude patients with bilateral structural disease.5,12,13 Since postmortem examination showed clinically unsuspected contralateral infarcts in some of these patients,14 both techniques should be used to rule out bilateral infarcts and/or contralateral extracranial occlusive disease, either of which might explain the observed contralateral flow reduction. Prior studies also never controlled for other determinants of rCBF such as age, blood pressure, hematocrit, arterial CO2, and risk factors for stroke.

We selected a patient population that allowed valid investigation of two questions: Is contralateral rCBF reduced in strictly unilateral stroke? If so, what factors are responsible?

Subjects and Methods

We identified 25 patients with nonhemorrhagic ischemic stroke through our PET data bank. As the nature of the study required rigorous selection, only 7 patients, all white men, were included in the final analysis. The selection criteria were 1) single unilateral supratentorial infarction as determined by clinical presentation, CT, and nuclear magnetic resonance imaging (NMRI) — patients who did not complete these studies or who had evidence of bilateral parenchymal disease were excluded; 2) absence of contralateral carotid disease as studied by conventional or intra-arterial digital subtraction angiography — minimal plaques at the carotid bifurcation were accepted, but nonstenotic ulcerative lesions and carotid stenoses of any degree led to exclusion from the study; 3) complete documentation of a risk factor profile — based on current criteria15 all patients were evaluated for cardiac disease, family history of stroke, smoking, hypertension, diabetes mellitus, gout, and elevated hematocrit, cholesterol, or lipids; and 4) stable cardiovascular and pulmonary conditions during rCBF measurements — no patient was in manifest cardiac failure or had arterial hypotension.

Regional Cerebral Blood Flow Measurement

The rCBF studies were carried out by the fluorine-18-fluoromethane (18FCH3) inhalation method using a single-slice Ortec ECAT-II PET scanner (Oak Ridge, Tenn.). The details of this method have been reported elsewhere.7,10-18 This technique allowed quantification of rCBF without invasive arterial blood sampling. Measured attenuation corrections were performed using a transmission scan with a germanium-68 ring source. Inhalation of 25-40 mCi of 18FCH3 was followed by 2 minutes of 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 at the normal level. A dynamic sequence of 8 1-minute emission scans was initiated at inhalation. The measured expired-breath activity curve constituted the input function used to derive best-fit rCBF (ml/100 g/min) and blood–brain partition coefficients. End-tidal expired gas measurements described the temporal behavior of the arterial ^18 FCH3 concentration, whereas venous blood samples provided the absolute scale. We recorded and averaged end-tidal CO₂ in each patient during the rCBF study.

A single horizontal emission scan was performed at the supratentorial level that showed the cerebral infarction on CT. The spatial resolution was 16 mm with a slice thickness of 18 mm. The rCBF data were computed for hemispheric mean flow (hCBF) on the ischemic (H_1) and contralateral sides (H_2). rCBF in the ischemic area (I) and its contralateral homologous counterpart (C) were also determined. Regions of interest were hand-drawn on the ischemic side based on qualitative inspection of the rCBF maps. The Ortec software automatically drew the contralateral, mirror-image regions of interest.

We did not normalize the rCBF values relative to Pco₂ because unpredictable individual CO₂ responses are known to occur in patients with cerebrovascular diseases. All rCBF and hCBF data were compared with values obtained from 13 neurologically normal controls. In our PET laboratory, the normal resting rCBF range was 34.1–51.3 ml/100 g/min (mean rCBF ± 2 SD, 95% confidence interval), the 95% confidence interval of Pco₂ being 26.7–41.3 mm Hg. Table 1 shows that patient Pco₂ was within normal limits.

### Data Analysis

The rCBF values were considered abnormal when they fell outside the 95% confidence interval of the controls. The small number of observations may have obscured a nonparametric data distribution. Therefore, for the purpose of multiple regression analysis, the normal distribution was achieved by transforming the data into their natural logarithms. Contralateral hCBF and rCBF were the dependent variables. We studied the following independent variables as possible predictors of contralateral hCBF and rCBF: ipsilateral rCBF in the ischemic area, Pco₂, mean arterial blood pressure (MABP, calculated as diastolic + (systolic – diastolic)/3), hematocrit, number of risk factors for stroke, time as days elapsed between stroke onset and rCBF measurement, and age. Multiple regression analysis determined the correlations between all variables. The F statistic was used to test the null hypothesis r = 0 at p < 0.05. We calculated the best-fit regression models and listed the p values of the alternative regression models. It was postulated that the absence of high, significant correlations would make a causative relation between variables highly unlikely, whereas the presence of such a correlation would permit speculation whether a causative relation exists.

### Results

Table 1 presents the details of the patient evaluation and the blood flow measurements. Figure 1 gives examples of the neuroimaging studies. Two patients (Patients 2 and 3) had ischemic strokes due to hemodynamically significant carotid disease of > 75% stenosis or total occlusion. Patient 6 suffered a cardioembolic stroke. The stroke pathogenesis in the remaining patients remained undetermined. Risk factor analysis showed the typical profile seen in most patients (Table 1). hCBF and rCBF were reduced below the 95% confidence interval bilaterally in 6 of 7 (86%) and 5 of 7 (71%) patients, respectively.

The results of the data analysis are shown in Tables 2 and 3. There were very strong, highly significant correlations between the ischemic region rCBF and both the contralateral hCBF (r = 0.944, p = 0.0014) and rCBF (r = 0.911, p = 0.0043). Figure 2 depicts the scattergrams and the best-fit regression models for our data. Pco₂, MABP, hematocrit, and time elapsed

### Table 1. Patient Data

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Angiogram (carotid circulation)</th>
<th>CT/NMRI</th>
<th>Days after onset</th>
<th>Risk factor profile</th>
<th>MABP (mm Hg)</th>
<th>Hct (%)</th>
<th>Pco₂ (mm Hg)</th>
<th>hCBF</th>
<th>rCBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L ICA plaque R normal</td>
<td>R MCA</td>
<td>83</td>
<td>6</td>
<td>3</td>
<td>31</td>
<td>29</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>L ICA occlusion R normal</td>
<td>L MCA</td>
<td>67</td>
<td>10</td>
<td>2</td>
<td>50</td>
<td>29.1</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>L ICA occlusion L normal</td>
<td>R MCA + ACA</td>
<td>52</td>
<td>12</td>
<td>4</td>
<td>110</td>
<td>31.7</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>R MCA</td>
<td>61</td>
<td>13</td>
<td>3</td>
<td>105</td>
<td>34.2</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>Bilateral plaques</td>
<td>R MCA</td>
<td>74</td>
<td>17</td>
<td>2</td>
<td>99</td>
<td>29.6</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>Normal</td>
<td>R MCA</td>
<td>56</td>
<td>28</td>
<td>4</td>
<td>101</td>
<td>29.9</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>Bilateral plaques</td>
<td>L MCA</td>
<td>61</td>
<td>47</td>
<td>1</td>
<td>110</td>
<td>39.0</td>
<td>33</td>
<td>35</td>
</tr>
</tbody>
</table>

Pt.: patient; CT., computed tomography; NMRI, nuclear magnetic resonance imaging; MABP, mean arterial blood pressure; Hct, hematocrit; Pco₂, carbon dioxide tension; hCBF, hemispheric mean flow in ml/100 g/min (H_1, ipsilateral; H_2, contralateral); rCBF, regional cerebral blood flow in ml/100 g/min (I, ipsilateral; C, contralateral); L, left; R, right; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; C, cardiac disease; D, diabetes mellitus; S, smoking; H, hypertension; F, family history.
after onset were not correlated with contralateral blood flow in any meaningful way. The risk factor profile and patient age were well correlated with both contralateral and ipsilateral blood flow (absolute value of $r$ 0.533–0.705). Table 3, however, shows that the alternative regression models for risk factors and age carried unacceptable probabilities of Type I error ($p > 0.7$).

Discussion

When compared with normal controls, blood flow contralateral to an ischemic focus was reduced in spite of apparent structural integrity in the contralateral hemisphere and carotid circulation. In contrast to Wise et al., we did not use asymptomatic controls with occlusive carotid disease since only 2 of our patients had relevant extracranial disease. Ideally, the control
group should match the patient population not only in age but also in risk factor profile and extent of cerebrovascular disease. Since asymptomatic subjects, however, usually do not undergo angiography in our institutions, such a control group is hardly possible. Therefore, we tried to control for both age and risk factor profile by including these into the multiple regression analysis.

All independent variables that might influence contralateral CBF were taken into consideration. The risk factor profiles were nonsignificantly correlated with blood flow in both hemispheres. Unexpectedly and in contrast to previous studies, there was a positive correlation between blood flow in both hemispheres and age. However, the high p value for Type I error indicated the fortuitous nature of this correlation. Other systemic determinants of rCBF, such as Pco2, MABP, and hematocrit, did not correlate with contralateral blood flow. The very strong and highly significant correlation between ipsilateral and contralateral blood flow in unilateral stroke indicates that rCBF in the ischemic region is the major determinant of contralateral blood flow. This appears to be the case as long as there is no contralateral parenchymal or occlusive disease.

What is the cause of the strong correlation between ipsilateral and contralateral blood flow? The possibility of a third, common variable fully explaining this correlation was excluded as multiple regression analysis did not reveal a common link among the other predictive variables tested. The partial correlation between risk factor profile and the flow reduction in both hemispheres might indicate that preexisting small vessel disease contributed to the high correlation of ipsilateral and contralateral rCBF. Multiple regression analysis, however, demonstrated that the degree of flow reduction in the stroke area was the principal and only significant factor. In addition, animal studies showed reduction of contralateral rCBF and metabolism in the absence of risk factors or preexisting vascular disease. Intracranial steal phenomena have been proposed as a possible explanation for contralateral flow reduction but would appear conceivable only in patients with significant carotid disease. Instead, blood flow in the contralateral hemisphere of 4 patients was significantly reduced although there was no occlusive arterial disease. Another alternative cause of generalized reduction in rCBF is increased intracranial pressure. This is an insufficient explanation in our series as we observed contralateral flow reduction in infarctions that did not display significant mass effect (Figure 1). Thus, we believe that transhemispheric diaschisis was the cause of the observed contralateral flow reduction.

The phenomenon of diaschisis was recently the subject of an excellent review. Neuronal inhibition appears to be mediated by deafferentation due to remote brain infarction. Based on Von Monakow's original description and Kempinsky's subsequent work, Feeney and Baron reemphasized "essential criteria" for diaschisis; these include a circumscribed injury, a neuronal basis for the depressive effects, occurrence at a distance from the lesion, identification of the fiber tracts involved, and a reversible process. In our patients these criteria, except for reversibility, were met. Unilateral brain infarction seemed to mediate contralateral hemispheric diaschisis through transcallosal commissure fibers. Reversibility, however, may not be an essential criterion as permanent diaschisis has been shown to occur in experimental studies.

### Table 2. Correlations of Contralateral Cerebral Blood Flow and Predictive Variables Determined by Multiple Regression Analysis

<table>
<thead>
<tr>
<th>Predictive variables</th>
<th>Contralateral</th>
<th>Ipsi-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hCBF rCBF</td>
<td>rCBF</td>
</tr>
<tr>
<td>Ipsilateral rCBF</td>
<td>0.944</td>
<td>0.911</td>
</tr>
<tr>
<td>Pco2</td>
<td>-0.327</td>
<td>-0.317</td>
</tr>
<tr>
<td>MABP</td>
<td>0.000</td>
<td>-0.175</td>
</tr>
<tr>
<td>Risk factors</td>
<td>-0.620</td>
<td>-0.705</td>
</tr>
<tr>
<td>Days after onset</td>
<td>0.217</td>
<td>0.124</td>
</tr>
<tr>
<td>Age</td>
<td>0.551</td>
<td>0.630</td>
</tr>
</tbody>
</table>

hCBF, hemispheric mean flow; rCBF, regional cerebral blood flow; Pco2, carbon dioxide tension; MABP, mean arterial blood pressure; Hct, hematocrit.

### Table 3. F-Statistic Probability Values for Multiple Regression Analysis on Contralateral Hemispheric and Regional Cerebral Blood Flow

<table>
<thead>
<tr>
<th>Predictive variables</th>
<th>hCBF p value</th>
<th>rCBF p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral rCBF</td>
<td>0.0014</td>
<td>0.0043</td>
</tr>
<tr>
<td>Pco2</td>
<td>0.9592</td>
<td>0.7480</td>
</tr>
<tr>
<td>MABP</td>
<td>0.7877</td>
<td>0.8282</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.3000</td>
<td>0.2122</td>
</tr>
<tr>
<td>Risk factors</td>
<td>0.7131</td>
<td>0.3394</td>
</tr>
<tr>
<td>Days after onset</td>
<td>0.5535</td>
<td>0.3394</td>
</tr>
<tr>
<td>Age</td>
<td>0.7439</td>
<td>0.8093</td>
</tr>
</tbody>
</table>

hCBF, hemispheric mean flow; rCBF, regional cerebral blood flow; Pco2, carbon dioxide tension; MABP, mean arterial blood pressure.
measurements in humans by Slater et al demonstrated reversible depression of contralateral hCBF, whereas Demeurisse et al found no resolution of the contralateral flow reduction. In our study, there was no correlation between contralateral blood flow and the time elapsed after stroke. This does not necessarily indicate that the depression of contralateral blood flow was irreversible since baseline rCBF might have been lower at onset. As only serial measurements could have studied reversibility, our method of data analysis does not allow further comments in this regard.

With these considerations in mind, we conclude that contralateral hCBF and rCBF were reduced in patients with strictly unilateral infarctions, and that transhemispheric diaschisis was the best explanation for this phenomenon. Systemic determinants of blood flow did not appear as important factors of contralateral flow reduction compared with the degree of flow impairment in the ischemic region.

References


KEY WORDS • regional cerebral blood flow • diaschisis • positron emission tomography • stroke

FIGURE 2. Results of multiple regression analysis. Left: Contralateral hemispheric mean blood flow (hCBF) vs. ischemic hCBF. Right: Contralateral regional cerebral blood flow (rCBF) vs. ischemic region-of-interest rCBF. Equations describe best-fit regression models.
Contralateral flow reduction in unilateral stroke: evidence for transhemispheric diaschisis.
H L Lagrèze, R L Levine, K L Pedula, R J Nickles, J S Sunderland and B R Rowe

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