Regional Cerebral Blood Flow in Chronic Stroke Patients

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Background and Purpose: The aim of this study was to investigate regional cerebral blood flow parameters during the postacute phase of unilateral ischemic stroke and to correlate them with clinical data.

Methods: Regional cerebral blood flow was measured in 187 patients in the stabilized phase of stroke by the xenon-133 inhalation method with 32 extracranial detectors. Thirty-eight patients were reexamined after a mean±SD time of 32±21.4 months.

Results: The overall detection of hypoperfusion was 92.0%, with asymmetries as the most sensitive index, especially for patients with a lesser degree of neurological disability. Neurological disability score was strongly associated with regional cerebral blood flow in the affected hemisphere (p<0.0001) and with asymmetries (p<0.0001). The presence of carotid obstruction further decreased the regional cerebral blood flow in the affected hemisphere and significantly increased asymmetry (p<0.0001). Subjects who had no hypoperfusion at absolute values analysis were more frequently free of carotid disease and had less severe disability than those who had bilateral or unilateral regional absolute cerebral blood flow reduction. In 38 patients without new cerebrovascular events, a significant (p=0.005) reduction of hemispheric regional cerebral blood flow asymmetries was found on a follow-up examination.

Conclusions: These data confirm the value of regional cerebral blood flow asymmetries in stroke detection and point out that important clinical information is also contained in absolute values analysis.

Key Words • cerebral blood flow • cerebral ischemia • xenon

Knowledge of the pathophysiology of focal cerebral ischemia has been growing since the most advanced technologies such as magnetic resonance imaging, cerebral blood flow (CBF), and metabolism measurement techniques have become available. Relations between regional cerebral blood flow (rCBF), glucose metabolism, and oxygen consumption and angiography, computed tomographic (CT) findings, and clinical outcome have been studied by methods based on the administration of xenon-133 and, more recently, by positron emission tomography.

The majority of these studies were carried out during the acute phase of stroke and were aimed at assessing the impact of drug regimens or surgical approaches on the evolution of stroke in the first few hours or days. In the postacute phase of stroke the use of brain structural imaging techniques is usually limited to the detection of new vascular episodes, whereas quantitative techniques such as CBF and metabolic measurements give information about the actual functional condition of both the stroke and the contralateral hemispheres. This information may be correlated with clinical data and be relevant to physicians engaged in the patient’s management.

We present here a retrospective analysis of unilateral, chronic stroke cases studied with the 133Xe inhalation method aimed at correlating rCBF findings with clinical parameters; preliminary data on an ongoing rCBF follow-up study are also reported.

Subjects and Methods

One hundred eighty-seven outpatients (135 men and 52 women, aged 18–84 years [mean±SD, 56.6±11.8 years]) were included in the study. They were selected from a group of >700 consecutive cerebrovascular cases and were diagnosed as affected by postacute ischemic stroke according to the following criteria: 1) a stabilized neurological deficit (>1 month since the acute event) attributable to a unilateral ischemic lesion as determined by clinical history and neurological examination; and 2) a cranial CT scan revealing hypodense supratentorial lesions in one hemisphere; patients with bilateral or infratentorial lesions were excluded.

One hundred thirty-seven (73.3%) patients had an ultrasound Doppler examination of neck vessels and/or angiography performed at different times after stroke and were classified in four subgroups according to the presence and type of obstruction. A complete obstruction or tight stenosis (>70%) of the carotid arteries to the stroked hemisphere was found in 54 (39.4%) cases, no major abnormalities in 73 (53.3%) patients, and in...
eight (5.8%) and in two (1.5%) patients, respectively, a bilateral or contralateral carotid obstruction was found. Only the first and the second subgroups were submitted to separate statistical analysis; the remaining patients were considered too few to be of statistical interest.

Neurological disability at the time of rCBF examination was graded according to the classification system of the Ad Hoc Committee on Cerebrovascular Diseases with the following scores: 0 indicates no clinical signs or symptoms, 1 indicates no significant impairment, and 2, 3, and 4 refer to mild, moderate, and severe impairment, respectively.

Thirty-eight patients (20.3%) (25 men and 13 women, aged 36–80 years [mean, 61.21 ± 9.34 years]) underwent a second rCBF examination 1–90 months (mean, 32 ± 21.4 months) after the first examination; all patients were regularly followed by our center and no patient had recurrent stroke or transient ischemic attack during the follow-up period. Three patients had no neurological disability on the first examination, four had a score of 1, 21 had a score of 2, eight had a score of 3, and two had a score of 4.

rCBF examinations were performed in the resting condition using a 32-probe (16 over each hemisphere) system, as described elsewhere. The clearance curves were subjected to a two-compartment analysis, but for the purpose of the present report the initial slope index (ISI) was used, which is one of the most reliable flow parameters in cerebral pathological conditions, since the partition coefficient of xenon for ischemic tissues (which is unknown) is not assumed when measuring the slope.

Expired end-tidal PCO2 (PETO2) was monitored throughout the examination and, as suggested by others, ISI values were not adjusted for individual PETO2 levels.

rCBF parameters computed for each patient included 1) regional absolute values (ReABS); 2) regional asymmetries (ReASY); 3) mean absolute hemisphere values (HeABSγ and HeABSs refer to the contralateral and stroked hemispheres, respectively); and 4) hemispheric asymmetry (HeASY).

Regional and hemispheric asymmetries were computed according to Mosmans et al:

\[ \text{ASY} = \frac{\text{ABSc} - \text{ABSs}}{\text{ABSc} + \text{ABSs}} \times 100 \]

where ABSs is the absolute value in the stroked hemisphere and ABSc is the absolute value in the contralateral hemisphere.

**Statistics**

rCBF data from 159 normal subjects defined as healthy on the basis of medical history and general medical and neurological examinations were used as a normative data base for statistical comparisons. They were divided into five control groups (one for each age decade from 20 to 60 and one from 60 to 80 years). The rCBF of each patient was compared with the age-matched control group by a Z statistic using a computer-assisted method developed in our laboratory and described in more detail elsewhere. A hypoperfused area was identified when rCBF values from at least two adjacent probes had z scores < -1.96 compared with control subjects.

The effects of duration of disease, age, and neurological disability at the moment of examination were studied by analyses of variance (ANOVAs) with the two absolute hemispheric values (HeABSc and HeABSs) and the HeASY as the dependent variables, age and duration of disease as regressors, and neurological disability score as a classification variable. In addition, the effect of obstruction of the neck vessels was investigated, introducing this variable in the ANOVA model as a classification variable for the smaller group of subjects when this information was available. ANOVAs were performed by the general linear models procedure of the software package SAS.

To assess the physiological significance of detection of hypoperfusion at ReABS analysis, we identified three hypoperfusion classes: unilateral, bilateral, and absent. We performed \( \chi^2 \) tests on the 3xn frequency tables with the hypoperfusion classes as the columns and the following categorical variables as the rows: location of the lesion (cortical or deep), neurological disability score, and the presence or absence of carotid obstruction. In the case of a significant result, further \( \chi^2 \)'s were performed in a post hoc fashion on two subtables that were obtained, respectively, by comparing the column that contributes most to the \( \chi^2 \) value with the sum of the remaining two columns, and by comparing the remaining two columns with one another. The resulting \( \chi^2 \) components indicate which class is different from the others.

In the patients who underwent two rCBF examinations, HeABSc, HeABSs, and HeASY at the two time points were compared by a paired t test. The correlation between differences in asymmetries and follow-up time between the two rCBF examinations was assessed by Pearson's r.

We report here all “nominal” p values, but we caution the reader that, because of testing for multiple hypotheses, one might reject the null hypothesis more confidently for levels of p ≤ 0.01.

**Results**

**Detection of the Infarcted Hemisphere and Association of rCBF Values With Other Variables**

Absolute values detected hypoperfused areas in 121 patients (64.7%): in 51 (27.3%) they were confined to the affected hemisphere, whereas they involved both hemispheres in 70 (37.4%).

Asymmetry values revealed significant hypoperfused regions within the stroked hemisphere in 153 patients (81.8%); in one patient a significant asymmetry in the contralateral hemisphere was found.

Of the remaining 33 cases (17.6%) undetected at asymmetry analysis, ReABS showed bilateral hypoperfusion in 11 cases (5.9%) and hypoperfusion in the stroked hemisphere in eight (4.3%), reaching an overall detection of 92%. In 14 patients (7.5%) no statistically significant rCBF abnormality was found.

Table 1 shows the prevalence of patients who had a significant hypoperfusion in the stroked hemisphere according to asymmetries and absolute values analysis for each neurological disability score category. asymmetry analysis was able to detect more patients with
significant hypoperfusion in the stroke hemisphere than absolute values for virtually all categories of neurological disability score. Both rCBF indexes increased their discrimination rate together with the increase in neurological disability score, except for the most severe group, in which the discrimination rate of ReASY was slightly lower than for moderate disability. The milder the neurological disability, the greater the difference in sensitivity of asymmetry analysis in comparison with absolute values analysis. The strongest difference in discrimination rate between the two flow indexes was seen in the group with no disability, in which ReABS showed hypoperfusion in the stroke hemisphere in 33.3% of cases and ReASY in 66.7%.

The mean rCBF in the stroke hemisphere (187 subjects) was strongly associated with neurological disability score and age (F=9.0 and 18.7, respectively; p<0.0001), whereas neurological disability score seemed to affect rCBF in the contralateral hemisphere less importantly (F=3.1, p<0.02). rCBF in both hemispheres was independent of duration of disease (F=0.4 for the affected hemisphere and F=0 for the unaffected hemisphere). Interhemispheric asymmetries were strongly dependent on neurological disability score (F=12.2, p<0.0001) but not on age or duration of disease (F=2.5 and F=3.4, respectively). Figure 1 shows the strong dependency of hemispheric asymmetry on neurological disability score.

When obstruction of the neck vessels was introduced as an independent variable (127 subjects; duration of disease was dropped because it was nonsignificant in the first analysis), age influenced both the unaffected and the affected hemispheres (p<0.0001), whereas both neurological disability score and carotid obstruction were associated with rCBF in the affected hemisphere (p<0.01) but had no influence on the unaffected one. Asymmetry values were not influenced by age, whereas both neurological disability score and carotid obstruction were associated with this rCBF parameter (p<0.0001).

The effect of age on the detection of hypoperfusion at ReABS was nonsignificant: the group with no hypoperfusion had a mean±SD age of 56.8±11.3 years, compared with the group with unilateral hypoperfusion at 55.5±13.3 years and those with bilateral hypoperfusion at 57.2±11.4 years.

There was weak evidence for a higher frequency of cortical versus subcortical infarctions (Table 2) in patients with unilateral hypoperfusion: χ²=7.1 (p<0.03) for the whole table, and χ²=5.7 (p<0.03) for the subtable comparing unilaterally hypoperfused patients with all the others.

Grades 3 and 4 of neurological disability score were found more frequently in the groups with unilateral or bilateral hypoperfusion (21.6% and 24.3%, respectively) compared with those with no hypoperfusion (7.6%). This is shown in Table 3 (p<0.0001).

A similar result was obtained for the presence of carotid obstruction (Table 4): there was a significantly higher percentage of patients with no obstruction in the group with no hypoperfusion (p<0.01), whereas bilateral and unilateral hypoperfusion did not differ in the prevalence of obstructed versus nonobstructed cases.

**rCBF Follow-up**

Mean blood flow in the stroke hemisphere did not significantly change between the first (41.99±5.69) and the second (42.31±7.12) examination; a slight but non-significant decrease was found for contralateral hemispheric blood flow (exam 1: 44.4±5.69; exam 2: 43.57±7.21; T=0.77). On the contrary, hemispheric asymmetries were significantly reduced (exam 1: 5.41±5.68; exam 2: 2.86±4.66; T=2.96, p=0.005). No correlation was found between differences in asymmetries and follow-up time between the two rCBF examinations.

**Discussion**

Before discussing our results, it should be noted that the group of patients we studied is not representative of the population of stroke patients. Indeed, most of our patients were seen on an outpatient basis, biasing our selection toward patients who had a greater probability of surviving a stroke (only seven of 187 subjects had severe residual disability, which carries higher mortality rates). Moreover, we excluded patients with hemorrhagic infarctions, who are known to have a more severe prognosis.

This study confirms that asymmetries are the most sensitive index for the detection of infarction for all degrees of neurological disability (Table 1). However, we
would also like to stress the importance of absolute values, which never gave false lateralizations. In the only falsely lateralized subject at asymmetries, Doppler examination showed an obstruction of the internal carotid on the side contralateral to the CT lesion.

Absolute rCBF values gave the opportunity to study the association of rCBF with age in both hemispheres (asymmetries are not correlated with age), finding no difference from normal subjects.23

Neurological disability score had a very significant association with rCBF asymmetries, but absolute rCBF in the affected hemisphere was also significantly correlated.

The presence of obstruction of the neck vessels did not modify the relation with age24 but had a significant effect on the stroke hemisphere, reducing its absolute values even further and significantly increasing the degree of asymmetry between the two hemispheres.2,22

In this group of subjects, the lower the asymmetry score, the better the clinical condition of the subject.

These data confirm the usefulness of absolute quantification of rCBF in stroke patients in the chronic phase.2,7 Whereas a unilateral reduction in absolute rCBF is the expected finding, we tried to detail further whether the presence of bilateral reduction of CBF or its absence was related to other clinical features of our patients.

Patients with no hypoperfusion at absolute values had significantly milder degrees of neurological disability (Table 3) and a lower incidence of carotid artery obstruction than hypoperfused patients (Table 4). Moreover, among those patients who were not hypoperfused either at absolute or at symmetry values analysis (14 cases), only one patient had major carotid pathology and none had neurological disability score >2. A score of 0 on the neurological disability score was found in 26.7% of these patients in comparison with 9.6% in the whole group.

Therefore, the absence of absolute hypoperfusion may be considered a reassuring finding for the physician and the patient. However, a doubt regarding the ability to detect deep infarctions may be raised.5 Indeed, the prevalence of deep infarctions was slightly higher in patients with normal or bilaterally reduced perfusion and lower in patients with unilateral hypoperfusion (Table 2). Therefore, absolute values are able to detect a substantial fraction of deep infarctions (51% altogether), especially when they have a generalized effect, possibly because of deafferentation of cortical structures.25,26

Bilateral rCBF reduction in stroke has been explained with three possible mechanisms: transneural depression,27–30 “interhemispheric steal,”28,31 and the presence of systemic vascular risk factors affecting both hemispheres.32 Although we were unable to test the last hypothesis, we showed in a previous report that hypertension can produce a bilateral reduction in rCBF, even in the absence of a stroke,33 and in the same line other authors showed that vascular risk factors can be a cause for rCBF reduction.34,35

The presence of carotid disease has been invoked to explain rCBF reduction in the contralateral hemisphere,25 producing transhemispheric “reverse steal,”35 but we found no difference in the incidence of carotid obstruction between bilaterally hypoperfused patients and those with unilateral hypoperfusion at absolute values analysis (Table 4). Moreover, Table 2 shows that bilateral hypoperfusion does not depend on the location of the lesion, because the ratio between deep and cortical infarctions in bilaterally hypoperfused patients is the same as in the whole group. Finally, Table 3 shows that there is no difference in clinical severity between unilateral and bilateral rCBF reduction. More research is

### Table 2. Frequency of Detection of Hypoperfused Areas at Absolute Values vs. Location of Infarction

<table>
<thead>
<tr>
<th>Infarct</th>
<th>None</th>
<th>Unilateral</th>
<th>Bilateral</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcortical</td>
<td>28 (41.8)</td>
<td>9 (18.4)</td>
<td>23 (32.4)</td>
<td>60 (32.1)</td>
</tr>
<tr>
<td>Cortical</td>
<td>39 (58.2)</td>
<td>40 (81.6)</td>
<td>48 (67.6)</td>
<td>127 (67.9)</td>
</tr>
<tr>
<td>Total</td>
<td>67 (100.0)</td>
<td>49 (100.0)</td>
<td>71 (100.0)</td>
<td>187 (100.0)</td>
</tr>
</tbody>
</table>

Whole table: $\chi^2 = 7.13$ ($p < 0.05$); unilateral vs. bilateral + none: $\chi^2 = 5.70$ ($p < 0.025$); normal vs. bilateral: $\chi^2 = 1.30$ ($p = NS$).

### Table 3. Frequency of Detection of Hypoperfused Areas at Absolute Values vs. Neurological Disability Score

<table>
<thead>
<tr>
<th>NDS</th>
<th>None</th>
<th>Unilateral</th>
<th>Bilateral</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12 (18.2)</td>
<td>1 (2.0)</td>
<td>5 (7.1)</td>
<td>18 (9.6)</td>
</tr>
<tr>
<td>1</td>
<td>19 (28.8)</td>
<td>13 (25.5)</td>
<td>10 (14.3)</td>
<td>42 (22.5)</td>
</tr>
<tr>
<td>2</td>
<td>30 (45.5)</td>
<td>26 (51.0)</td>
<td>38 (54.3)</td>
<td>94 (50.3)</td>
</tr>
<tr>
<td>3–4</td>
<td>5 (7.6)</td>
<td>11 (21.6)</td>
<td>17 (24.3)</td>
<td>33 (17.6)</td>
</tr>
<tr>
<td>Total</td>
<td>66 (100.0)</td>
<td>51 (100.0)</td>
<td>70 (100.0)</td>
<td>187 (100.0)</td>
</tr>
</tbody>
</table>

NDS, neurological disability score.

Whole table: $\chi^2 = 18.57$ ($p < 0.005$); normoperfused vs. hypoperfused: $\chi^2 = 15.91$ ($p < 0.001$); unilateral vs. bilateral: $\chi^2 = 3.70$ ($p = NS$).
needed to identify the causes and correlates of bilateral reduction of rCBF.

Although the duration of disease had a nonsignificant relation with rCBF in the whole sample of stroke patients, in the subgroup of 38 patients undergoing a second rCBF examination after a mean time of almost 3 years, a significant reduction of interhemispheric asymmetries was seen, due to a slight CBF decrease in the nonstroked hemisphere together with an increase in the stroked hemisphere, both of which were not statistically significant. This is in disagreement with Veering et al., who found a nonsignificant increase in asymmetries in 51 patients evaluated on admission and 3 months later. However, our group was studied much later in the course of the disease, and we show here that, at least in those patients with a relatively mild presentation of the disease (73.6% of the sample had a neurological disability score between 0 and 2), a redistribution of flow to the advantage of the stroked hemisphere occurred. However, this compensation mechanism does not depend on time, at least in a continuous fashion. It might be a consequence of other factors such as type of therapy, compliance of the patient, or physical activity. More information on this sample of patients will be provided in a future study. However, these findings might be an indication that prognosis is favorable in those patients who show a decrease of asymmetries (we had no reinfarctions in this sample) and that, conversely, an increase in asymmetries over time should prompt further investigation and may indicate an impairment of hemodynamic compensatory mechanisms.

In conclusion, rCBF evaluation in terms of asymmetry values has many advantages, but important information is contained in absolute values, which can be obtained noninvasively and inexpensively only by using freely diffusible tracers such as $^{133}$Xe.

Preliminary follow-up data suggest that, in the absence of recurrent cerebral ischemia, hemispheric asymmetries tend to decrease with time, probably as a result of a new cerebral homeostasis.

### References

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Stroke. 1993;24:94-99
doi: 10.1161/01.STR.24.1.94
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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