Remote Effect of Deep-Seated Vascular Brain Lesions on Cerebral Blood Flow

Ezzedine Attig, MD, André Capon, MD, Guy Demeurisse, MD, and Michel Verhas, MD

We measured regional cerebral blood flow using the xenon-133 inhalation method, at approximately 1 month after onset, in 60 stroke patients who had no evidence of major carotid artery stenosis or occlusion. Their single lesions (43 infarcts and 17 hematomas) were located in the capsulothalamolenticular region, sparing the cortex. Hemispheric mean cerebral blood flow was reduced on the side of the lesion in 25 patients and on both sides in 20. Regional hypoperfusion was observed in 46 patients (ipsilaterally in 34, bilaterally in 10, and contralaterally in two). Regional hypoperfusion was observed most frequently in the frontal lobe, particularly in the motor and premotor cortices of the prerolandic area. The 46 patients with regional hypoperfusion were compared with the 14 patients without regional hypoperfusion, considering the size and location of the lesion as well as the functional and analytic motor performances. As a rule, the lesion was slightly smaller and more posterior and the functional (p<0.001) and analytic (p<0.05) motor performances were significantly better in the 14 patients without regional hypoperfusion. Since the xenon-133 inhalation method examines cortical blood flow, we can attribute blood flow reductions resulting from deep-seated lesions to a functional depression akin to diaschisis. Interpretation of the clinical consequences and pathogenesis of this phenomenon requires further sequential and pathologic studies. (Stroke 1990;21:1555-1561)

Among patients with regional hypoperfusion, we then preliminarily analyzed the relation between the degree and extent of this hypoperfusion and motor performance.

Subjects and Methods

We identified during the acute or subacute stage 60 consecutive stroke patients (28 men and 32 women) suffering from a first and single deep hemispheric vascular lesion sparing the cortex. Their mean±SD age was 65.5±13.1 (range 27-83) years. Their lesions (hematoma in 17 and infarct in 43 [including three lacunes]) were located on the right side in 34 patients and on the left side in 26. Eighteen patients with an infarct had intravenous digital subtraction angiography (IV-DSA) of the supra-aortic arteries. All patients underwent hemodynamic vascular examinations with continuous-wave Doppler ultrasound and \[^{99m}Tc\]pertechnetate brain radioangiography. In our experience, these examinations can detect internal carotid artery occlusion in 95% of cases.\(^{17,18}\) The IV-DSA and Doppler examinations were performed a mean±SD of 32.8±18.9 (range 5-81) days after the stroke. Patients with evidence of a major carotid stenosis or occlusion were excluded. The controls comprised 39 active volunteers (22 men and 17 women) free of major cerebrovascular risk factors. Their mean±SD age was 39.9±14.4 (range 20-74) years.

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All patients and controls underwent rCBF measurements using the xenon-133 inhalation technique. Theoretical aspects and limitations of this method have been described elsewhere. Only a brief consideration will be given here. The rCBF was measured in 16 regions on either side of the head by 32 detectors precisely positioned in relation to the orbitomeatal line. The results were expressed as the initial slope index (ISI) representing mainly blood flow of the cortical gray matter. In each detector, rCBF was obtained as a raw value and its relative value (percentage of the total hemispheric mean cerebral blood flow [CBF]) was calculated. These results were corrected for the air passage artifact and for PCO2 estimated from recordings of end-tidal CO2 concentration (ISI correction factor at rest 1.4%/mm Hg). The ISI is independent of the blood partition coefficient. In our study, PCO2 and hemoglobin concentration were similar in all subgroups of patients and in the controls. The advantages of the xenon-133 inhalation method are 1) its relative stability under pathologic conditions and at low counts, 2) its reliability (test–retest reproducibility), and 3) its quantification of rCBF data. Its limitations are 1) its weak spatial resolution (25 mm), 2) the "look-through" phenomenon, and 3) the "cross-talk" effect. In our study, the look-through phenomenon was negligible because of the minimal contribution of the subcortical compartment to the low-energy emissions of xenon-133. The cross-talk effect, which causes underestimation of true hemispheric blood flow asymmetries, was minimized by the use of relative values of rCBF.

Hemispheric mean CBF hypoperfusion was defined as values two standard deviations (2 SDs) under the value in an age-matched subgroup of controls. For regional hypoperfusion, the same criterion, 2 SD under the normal relative value in a given detector, was used. In the controls, no individual relative value was less than 2 SD in most detectors, particularly those detectors showing hypoperfusion in the patients. Relative hyperperfusion was not considered.

The clinical evaluation included a neurologic examination and measures of motricity (six movements of the upper and lower limbs, or analytic motor performance, with scores ranging from 0 to 100 and functional independence (independence in walking and activities of daily living, or functional motor performance) with scores ranging from 0 to 100.

The lesion was documented by computed tomography (CT) with a third-generation device and slices 1 cm thick parallel to the orbitomeatal line in all patients. In each slice, the contours of the hematoma, infarct, or lacune (morphologically defined as a lesion of <15 mm3) were redrawn on a digitizing table and stored in a computer and the surface area of the lesion was calculated. In each patient, the total size of the lesion was estimated by a volumetric index (VI). In each slice, the lesion volume was considered to be the product of the surface area x 1 cm. The sum of the lesion’s volumes in different slices determined the VI for each patient. The average location of lesions in subgroups of patients with or without regional hypoperfusion was defined with a computed graphical procedure that superimposes the locations of all lesions and determines their frequencies (25–50% and >50% of cases) in two concentric subregions of each slice.

Statistical analysis was achieved by using paired and unpaired t tests, one-way analysis of variance, and the Student-Newman-Keuls test. The normality of the distribution of our data was evaluated by the standardized kurtosis coefficient. Results are given as mean ± SD.

Results

In the controls, the effect of age on hemispheric mean CBF (as ISI) assessed in three subgroups (subgroup 1: n=18, age 26.9±3.9 [range 20–35] years; subgroup 2: n=12, age 41.7±4.8 [range 36–49] years; subgroup 3: n=9, age 60.2±8.4 [range 52–74] years) showed a significant decrease after the age of 50 (hemispheric mean CBF 67.9±10.1 [range 49.7–88.4], 67.1±9.5 [range 53.1–80.2], and 54.2±8.3 [range 40.7–68.1] for subgroups 1, 2, and 3, respectively; p<0.005). Concerning the effect of age on distributions of rCBF, each detector’s mean value was compared among the three control subgroups. Only two detectors on each side had rCBF values slightly but significantly decreased in the prerolandic area. This was particularly true when subgroups 2 and 3 (three detectors) were compared.

In the patients, the delays in days from stroke to the rCBF measurements (Tables 1 and 2) and the motor performance (Table 2), CT (Tables 1 and 2), and Doppler and/or IV-DSA examinations were similar in all subgroups. The subgroup of 17 patients with a hematoma and the subgroup of 43 patients with an infarct did not differ significantly (Table 1). Their hemispheric mean CBF values (as ISI) were less than age-matched normal values (54.2±8.3, range 40.7–68.1) on the side of the lesion in 25 patients and on both sides in 20. The ipsilateral hemispheric mean CBF was significantly lower than the contralateral value in all patients (Tables 1 and 2, p<0.0005), even in those without regional hypoperfusion (Table 2, p<0.01).

Regional hypoperfusion was absent in 14 patients and present in 46 (ipsilaterally in 34, bilaterally in 10, and contralaterally in two). Cortical hypoperfusion predominated in the frontal lobe, particularly in the motor and premotor areas (Figure 1). Compared with the subgroup of 14 patients without regional hypoperfusion, the subgroup of 46 patients with regional hypoperfusion (Table 2) had 1) a larger lesion (p<0.001), 2) lower mean ipsilateral (p<0.0125) and contralateral (p<0.05) hemispheric mean CBF values, and 3) reduced scores for analytic (p<0.05) and functional (p<0.001) motor performance. Comparison of the computed average location of the lesion in the two subgroups showed that the lesion was smaller and located slightly more posteriorly in the patients without regional hypoperfusion (Figure 2A).
To analyze the relation between the size of the lesion and the occurrence and extent of regional hypoperfusion, we categorized the patients arbitrarily as having small (including lacunes), medium-sized, or large lesions (Table 3). Regional hypoperfusion occurred in all patients with medium-sized and large lesions, but in only 20 of 34 with small infarcts (including the three with lacunes). The size of the hypoperfused area (number of detectors showing hypoperfusion) increased nonsignificantly with the size of the lesion (Table 3). Therefore, we further divided the 46 patients with regional hypoperfusion into subsubgroups according to the number of detectors showing hypoperfusion (subsubgroup I, one or two detectors; subsubgroup II, three detectors; subsubgroup III, four to eight detectors). Table 4 shows that lesion size increased significantly \( p<0.05 \) between subsubgroup I and subsubgroup II or III. Ipsilateral hemispheric mean CBF decreased from subsubgroup I to III, but only the value in subsubgroup III differed significantly \( p<0.05 \) from that in subsubgroup I or II. Concerning the analytic motor performance, Table 4 shows the same trends, with the score in subsubgroup III significantly lower than that in subsubgroup I \( p<0.01 \) or II \( p<0.05 \).

**Discussion**

In our controls, volunteers free of major cerebrovascular risk factors, there was a significant decrease in hemispheric mean CBF measured using xenon-133 inhalation with age, compatible with findings in the literature.\(^{29,30}\) We defined normal hemispheric mean CBF in relation to values in age-matched subgroups of the controls. For the determination of regional hypoperfusion, our comparison with younger controls was justified because in them age failed to show major effects on the rCBF landscape, whereas our results showed clear and large rCBF reductions, predominantly in the central and precentral regions. This is compatible with the statement of Frackowiak in a recent review: \(^{31}\) "In general regional studies failed to resolve the question whether normal ageing was inevitably associated with a decline in cerebral perfusion." The use of a relative value of rCBF, which is independent of CBF level, is another argument. However, a possible limitation of

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### Table 1. Comparison Between Patients With Hematoma and Infarct

<table>
<thead>
<tr>
<th>Lesion</th>
<th>( n )</th>
<th>Age (years)</th>
<th>Computed tomography</th>
<th>CBF measurement</th>
<th>Hemispheric mean CBF (ISI)</th>
<th>Regional hypoperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma</td>
<td>17</td>
<td>65.6±13.1</td>
<td>33.3±21.1</td>
<td>34.9±19.7</td>
<td>39.1±9.0</td>
<td>15/88</td>
</tr>
<tr>
<td>Median</td>
<td>69</td>
<td>26</td>
<td>76</td>
<td>28</td>
<td>37.9</td>
<td>3</td>
</tr>
<tr>
<td>Range</td>
<td>42–83</td>
<td>6–74</td>
<td>15–70</td>
<td></td>
<td>25.2–54.2</td>
<td>1–5</td>
</tr>
<tr>
<td>Infarct</td>
<td>43</td>
<td>65.4±13.2</td>
<td>26.4±19.4</td>
<td>32.4±15.6</td>
<td>39.9±8.3</td>
<td>31/72</td>
</tr>
<tr>
<td>Median</td>
<td>68</td>
<td>21</td>
<td>27</td>
<td></td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td>Range</td>
<td>27–83</td>
<td>6–94</td>
<td>11–64</td>
<td></td>
<td>24.8–65.4</td>
<td>1–8</td>
</tr>
</tbody>
</table>

**TABLE 1.** Comparison Between Patients With Hematoma and Infarct

CBF, cerebral blood flow. No significant differences between patients with hematoma and infarct by unpaired t test (by \( x^2 \) test for number of patients with regional hypoperfusion).

\(^{*}p<0.0005 \) different from ipsilateral by paired \( t \) test.

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**FIGURE 1.** Schematic representation of 32 regional cerebral blood flow detectors in both lateral views, with spatial relations between detectors and underlying brain structures. Frequency of hypoperfusion (in percentage of 34 patients with left and of 26 patients with right hemispheric lesion; contralateral hypoperfusion not considered) is shown for each detector. Cortical hypoperfusion predominates in frontal lobe, particularly in motor and premotor cortices (detectors 4 and 7 in right hemisphere and detectors 20, 21, and 23 in left hemisphere).
Hemispheric mean CBF was decreased ipsilaterally in 42% and bilaterally in 33% of our patients. The ipsilateral value was almost always lower (with a high degree of significance) than the contralateral value, even in patients without regional hypoperfusion. This asymmetric but bilateral reduction of hemispheric mean CBF in patients with well-documented unilateral brain lesions has been known for our method was the lack of a control subgroup with vascular risk factors.

In our patients, CBF data were obtained 1 month after the stroke to avoid the management difficulties frequently encountered during the acute stage and the interference of cerebral edema or intracranial hypertension.

Hemispheric mean CBF was decreased ipsilaterally in 42% and bilaterally in 33% of our patients. The ipsilateral value was almost always lower (with a high degree of significance) than the contralateral value, even in patients without regional hypoperfusion. This asymmetric but bilateral reduction of hemispheric mean CBF in patients with well-documented unilateral brain lesions has been known for

| Table 3. Occurrence of Regional Hypoperfusion in Patients With Small, Medium-Sized, and Large Lesions |
|-----------------------------------------------|----------|-----------|------------------|
| Lesion size | n | VI | Patients | Regional hypoperfusion | Detectors/patient |
| Small | | | | | |
| Mean±SD | 3.36±1.63 | 20 | 59 | 2.5±1.9 |
| Median | 3.14 | | 2 | |
| Range | 1.10–6.88 | | | 1–8 |
| Medium | | | | | |
| Mean±SD | 9.69±1.34 | 14 | 100 | 3.0±1.4 |
| Median | 9.77 | | 3 | |
| Range | 7.69–11.89 | | | 1–6 |
| Large | | | | | |
| Mean±SD | 16.21±4.10 | 12 | 100 | 3.8±2.0 |
| Median | 14.84 | | 3 | |
| Range | 12.09–24.62 | | | 1–7 |

VI, volumetric index. Small lesions include three lacunes. All differences among categories in VI were significant (p<0.05) by Student-Newman-Keuls test.
years32-37 and was recently confirmed38 but also
denied39 by PET measurements.

Regional hypoperfusion was observed ipsilaterally in
57% of our patients, contralaterally in 3%, and
bilaterally in 17%. Because of the low energy of the
isotope, the bidimensional xenon-133 inhalation
method (using ISI) measures almost exclusively cor-
tical blood flow. Our findings must then be consid-
ered as remote effects of deep-seated hemispheric
lesions. These localized reductions of rCBF in mor-
phologically intact cortical regions were mentioned
recently in the literature. Orgogozo et al41 first de-
scribed this phenomenon in a series of six patients. It
was later confirmed by various functional methods
applied to series of patients not exceeding 18 (rang-
ing from one to 18) and by ourselves in a prelimi-
ary study on 28 aphasic patients.7

Regional hypoperfusion was present in approxi-
mately three fourths of our current patients. The
proportion of patients with regional hypoperfusion
increased with the size of the lesion, although hypo-
perfusion was observed in all three patients with
lacunes located in the posterior part of the capsu-
lothalamic region. The absence of cortical hypoper-
fusion in nearly one quarter of our patients (most
with a small lesion) possibly resulted from the poor
spatial resolution (25 mm) of the xenon-133 inhala-
tion method (limited cortical hypoperfusion could
have been masked by the normal perfusion of neigh-
broring areas).

Two hypotheses could explain the remote effect of
deep-seared lesions. The first is hemodynamic: the
“penumbra zone” surrounding the lesion40,41 could
reach the cortex and induce the observed hypoper-
fusion. The rCBF in this zone is not sufficiently
reduced to cause tissue necrosis and be disclosed by
CT. This hypothesis is unsatisfactory for various
reasons. The penumbra is present only during the
acute phase (an area of misery perfusion correspond-
ing to the penumbra lasts not later than the twelfth
day according to Baron et al42,45), and our rCBF
measurements were performed later. Moreover, this
hypothesis would not account for extension of the
hypoperfused area toward the frontal pole and cer-
tainly not for hypoperfusion in the contralateral
hemisphere. In addition, this hypothesis, supported
by Skyhøj Olsen et al46 in cases with arterial occlusion,
should be discarded in patients with hematoma (15 of
our 17 patients with a hematoma showed regional
hypoperfusion) and in most of our patients with an
infarct, especially those studied with IV-DSA (18
cases). Another hemodynamic hypothesis is the pos-
sible existence in some patients of delayed cortical
misery perfusion, chronically reduced CBF rarely
described in cases of either carotid or middle cer-
bral artery (MCA) occlusion.44-46 In our patients it is
unlikely that a carotid occlusion existed, but MCA
stenosis or occlusion, recanalized or not,46 may have
occurred in some of our patients with an infarct,
indicating inadequate perfusion distal to the MCA.
The second hypothesis is that cortical hypoperfusion
results from a functional reduction in cortical neu-
ronal activity. Indeed, the close relation between
neuronal activity, local metabolism, and CBF has
been clearly demonstrated in normal persons47-51 as
well as in stroke patients studied after the acute
stage.52,53 The reduction of cortical metabolism in the
case of deep hemispheric lesions demonstrated by
PET in humans10-14 and by autoradiography in rats54,55 is a strong argument in favor of this second
hypothesis.

In our patients, there was a significant influence of
the lesion’s size on both motor performance and
cortical rCBF. The motor dysfunction is classically
attributed to the interruption of the pyramidal tract.
The localization of cortical hypoperfusion predomi-
nantly in the motor and premotor regions suggests a
possible relation with motor dysfunction. Cortical

<table>
<thead>
<tr>
<th>Subsubgroup</th>
<th>n</th>
<th>Age (years)</th>
<th>Lesion size (cm³)</th>
<th>Hemispheric mean cerebral blood flow (ISI)</th>
<th>Motor performance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ipsilateral</td>
<td>Contralateral</td>
</tr>
<tr>
<td>I</td>
<td>11</td>
<td>68.7±13.0</td>
<td>6.04±4.68</td>
<td>41.0±8.9*</td>
<td>42.6±9.0</td>
</tr>
<tr>
<td>Median</td>
<td>74</td>
<td>4.43</td>
<td></td>
<td>38.3</td>
<td>40.5</td>
</tr>
<tr>
<td>Range</td>
<td>44-83</td>
<td>1.1-17.7</td>
<td></td>
<td>31.8-65.4</td>
<td>33.6-64.6</td>
</tr>
<tr>
<td>II</td>
<td>16</td>
<td>61.4±15.2</td>
<td>10.75±7.15*</td>
<td>39.5±6.6*</td>
<td>41.9±7.9</td>
</tr>
<tr>
<td>Median</td>
<td>61.5</td>
<td>10.19</td>
<td></td>
<td>39</td>
<td>41.4</td>
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<tr>
<td>Range</td>
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<td></td>
<td>25.5-53.2</td>
<td>25.6-58.0</td>
</tr>
<tr>
<td>III</td>
<td>19</td>
<td>68.9-10.3</td>
<td>10.37±4.68*</td>
<td>32.5±7.1</td>
<td>35.5±6.7</td>
</tr>
<tr>
<td>Median</td>
<td>69</td>
<td>10.6</td>
<td></td>
<td>30.8</td>
<td>34.5</td>
</tr>
<tr>
<td>Range</td>
<td>45-81</td>
<td>2.32-17.39</td>
<td></td>
<td>24.8-48.2</td>
<td>26.6-46.0</td>
</tr>
</tbody>
</table>

Subgroup I, one or two detectors showing hypoperfusion; subgroup II, three detectors showing hypoperfusion; subgroup III, 4-8 detectors showing hypoperfusion. ISI, initial slope index.

*tp<0.05, 0.01, respectively, different from remaining subsubgroup by one-way analysis of variance and Student-Newman-Keuls test.
hyperperfusion, significantly related to size of the lesion and severity of the motor dysfunction, is compatible with this suggestion. The fact that, among the motor performances, the functional index was significantly more reduced in patients with regional hyperperfusion than the analytic index suggests the role played by other clinical parameters. Indeed, the functional index is also dependent on other associated deficits (e.g., sensory and cognitive disturbances). These impairments, not specially studied in this work, may be considered a further consequence of the regional hyperperfusion. In cases of deep hemispheric insult, this new interpretation of neuropsychologic disturbances was suggested by most of the observations of memory, neglect, or aphasic disorders. Nevertheless, these interesting considerations must be taken cautiously because no definite correlation, in large series, has been established until now. Our preliminary analysis of the relation between the extent of regional hyperperfusion and the severity of clinical deficit showed that only the extent of regional hyperperfusion was related to the severity of analytic motor performance.

In summary, we studied 60 patients suffering from a unilateral deep vascular brain lesion sparing the cortex and confirmed the occurrence of a significant reduction in cortical rCBF. The regional hyperperfusion (in 77% of our patients) was predominant in the prerolandic area. The most likely explanation for this remote effect on rCBF is a functional depression of neuronal activity (diaschisis), but we cannot firmly exclude the possible role of delayed misery perfusion in some patients with an infarct. The precise mechanism of this phenomenon is not yet known, but it could be the result of deifferentiation and/or degeneration. We think that a transneural depression of metabolism is the initial mechanism, after which degeneration may occur depending on the importance (number of damaged fibers) and the quality (preferential connections) of the distal cortical disconnections. To our knowledge, there is no pathologic report of neuronal loss and atrophy within the distant hypoperfused area until now. To better define the clinical consequences (sensory, motor, ataxic, neuropsychologic, and dysphasic disturbances) and the pathogenesis of the cortical rCBF reductions, it would be interesting to further analyze, in a large sequential study, the possible relations among the lesion location, the clinical parameters, and the resulting cortical rCBF reduction in relation to its site, duration, and reactivity to functional stimulation.

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61. Attig et al: Cortical rCBF in Deep Brain Lesions

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