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 capsulothalamicentricular 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)

In patients suffering from a deep-seated hemispheric vascular lesion, measurements often disclose areas of reduced regional cerebral blood flow (rCBF) in the cortex. This intriguing remote effect of the lesion has been mentioned by various authors, generally in short series of patients, and studied using various methods including intracarotid,1–5 intravenous,6 or inhaled7 xenon-133 and single-photon emission computed tomography8,9 or positron emission tomography (PET).10–14 The remote effect has been observed not only in the cortex, but also in the contralateral cerebellum.15,16 and has generally been interpreted as a depression of neuronal function of the diaschisis type.

Our present work concerns a series of 60 patients with a deep-seated infarct, hematoma, or lacune. To analyze the mechanism of the remote effect of these lesions on cortical perfusion, we compared patients with and without decreased cortical rCBF.

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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 [99mTc]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.
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 recordins 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 motor performance). Comparisons 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.

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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
FIGURE 2. Computed average location and size of lesion in two transverse sections through basal ganglia (A) and junctional zone (B) levels. Regardless of actual side of the lesion, all patients with cortical hypoperfusion are represented on the right side and those without cortical hypoperfusion are represented on the left side. In black: topography of lesions common to >50% of patients; in white: topography of lesions common to 25–50% of patients.

TABLE 2. Comparison Between Patients With and Without Regional Hypoperfusion

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Age (years)</th>
<th>Cerebral blood flow</th>
<th>Motor performance</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Delay (days)</td>
<td>Hemispheric mean (ISI)</td>
<td>Delay (days)</td>
</tr>
<tr>
<td>Without regional hypoperfusion</td>
<td>14</td>
<td>62.0±12.3</td>
<td>44.1±7.2</td>
<td>44.8±7.3*</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>31.9±17.3</td>
<td>26</td>
<td>40.9</td>
<td>41.7</td>
</tr>
<tr>
<td>Median</td>
<td>42–83</td>
<td>11–64</td>
<td>35.7–62.2</td>
<td>36.5–64.0</td>
</tr>
<tr>
<td>Range</td>
<td>27–83</td>
<td>13–70</td>
<td>24.8–65.4</td>
<td>25.6–64.6</td>
</tr>
<tr>
<td>With regional hypoperfusion</td>
<td>46</td>
<td>66.5±13.2</td>
<td>33.5±16.7</td>
<td>40.6±8.5‡</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>3.36±1.63</td>
<td>28</td>
<td>37.7</td>
<td>39.7</td>
</tr>
<tr>
<td>Median</td>
<td>71.5</td>
<td>10</td>
<td>3.0±1.4</td>
<td>3.8±2.0</td>
</tr>
<tr>
<td>Range</td>
<td>27–83</td>
<td>13–70</td>
<td>24.8–65.4</td>
<td>25.6–64.6</td>
</tr>
</tbody>
</table>

No significant differences between means of delays in cerebral blood flow, motor performance, and lesion measurements in patients with or without regional hypoperfusion (six groups) by one-way analysis of variance (F=0.50, p=0.776); no significant differences between means of age. ISI, initial slope index.

$ p<0.01; \$ p<0.005, respectively, different from ipsilateral by paired t test.
††† p<0.0125, 0.05, 0.001, respectively, different from without hypoperfusion by Student’s unpaired t test.

TABLE 3. Occurrence of Regional Hypoperfusion in Patients With Small, Medium-Sized, and Large Lesions

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. (%)</th>
<th>Patients</th>
<th>Regional hypoperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without regional hypoperfusion</td>
<td>20 (59)</td>
<td>2</td>
<td>12 (2)</td>
</tr>
<tr>
<td>With regional hypoperfusion</td>
<td>14 (31%)</td>
<td>2</td>
<td>2 (1–6)</td>
</tr>
</tbody>
</table>

No significant differences among categories in VI were significant (p<0.05) by Student-Newman-Keuls test. VI, volumetric index. Small lesions include three lacunes. All differences among categories in VI were significant (p<0.05) by Student-Newman-Keuls test.

* p<0.01; ** p<0.005, respectively, different from ipsilateral by paired t test.
††† p<0.0125, 0.05, 0.001, respectively, different from without hypoperfusion by Student’s unpaired t test.

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. This ipsilateral value was 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 several years. The ipsilateral value was 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 several years.
years and was recently confirmed but also denied 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 cortical blood flow. Our findings must then be considered as remote effects of deep-seated hemispheric lesions. These localized reductions of rCBF in morphologically intact cortical regions were mentioned recently in the literature. Orgogozo et al first described this phenomenon in a series of six patients. It was later confirmed by various functional methods applied to series of patients not exceeding 18 (ranging from one to 18) and by ourselves in a preliminary study on 28 aphasic patients.

Regional hypoperfusion was present in approximately three fourths of our current patients. The proportion of patients with regional hypoperfusion increased with the size of the lesion, although hypoperfusion was observed in all three patients with lacunes located in the posterior part of the capsularthalamic region. The absence of cortical hypoperfusion 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 inhalation method (limited cortical hypoperfusion could have been masked by the normal perfusion of neighboring areas).

Two hypotheses could explain the remote effect of deep-seated lesions. The first is hemodynamic: the "penumbra zone" surrounding the lesion could reach the cortex and induce the observed hypoperfusion. 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 corresponding to the penumbra lasts not later than the twelfth day according to Baron et al), and our rCBF measurements were performed later. Moreover, this hypothesis would not account for extension of the hypoperfused area toward the frontal pole and certainly not for hypoperfusion in the contralateral hemisphere. In addition, this hypothesis, supported by Skyhøj Olsen et al 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 possible existence in some patients of delayed cortical misery perfusion, chronically reduced CBF rarely described in cases of either carotid or middle cerebral artery (MCA) occlusion. In our patients it is unlikely that a carotid occlusion existed, but MCA stenosis or occlusion, recanalized or not, 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 neuronal activity. Indeed, the close relation between neuronal activity, local metabolism, and CBF has been clearly demonstrated in normal persons as well as in stroke patients studied after the acute stage. The reduction of cortical metabolism in the case of deep hemispheric lesions demonstrated by PET in humans and by autoradiography in rats 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 predominantly in the motor and premotor regions suggests a possible relation with motor dysfunction. Cortical

### Table 4. Comparison Among Subsubgroups of Patients According to Extent of Regional Hypoperfusion

<table>
<thead>
<tr>
<th>Subsubgroup</th>
<th>( n )</th>
<th>Age (years)</th>
<th>Lesion size (cm²)</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>Subgroup 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>38.3</td>
<td>40.5</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>44–83</td>
<td>1.1–17.7</td>
<td>31.8–64.0</td>
<td>33.6–64.6</td>
<td></td>
</tr>
<tr>
<td>Subgroup 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>Mean±SD</td>
<td></td>
<td>61.5</td>
<td>10.19</td>
<td>39</td>
<td>41.4</td>
</tr>
<tr>
<td>Median</td>
<td>27–77</td>
<td>1.14–24.62</td>
<td>25.5–53.2</td>
<td>25.6–58.0</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>45–81</td>
<td>2.32–17.39</td>
<td>24.8–48.2</td>
<td>26.6–46.0</td>
<td></td>
</tr>
<tr>
<td>Subgroup 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>Mean±SD</td>
<td></td>
<td>69</td>
<td>10.6</td>
<td>30.8</td>
<td>34.5</td>
</tr>
<tr>
<td>Median</td>
<td>45–81</td>
<td>2.32–17.39</td>
<td>24.8–48.2</td>
<td>26.6–46.0</td>
<td></td>
</tr>
</tbody>
</table>

*\( p<0.05, 0.01, \) respectively, different from remaining subsubgroup by one-way analysis of variance and Student-Newman-Keuls test.
hypoperfusion, 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 hypoperfusion 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 hypoperfusion. 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 hypoperfusion and the severity of clinical deficit showed that only the extent of regional hypoperfusion 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 hypoperfusion (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 deafferentation 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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References


**Key Words** • cerebral blood flow • diaschisis • hemiplegia • xenon

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