Vascular Response to Carbon Dioxide in Areas With and Without Diaschisis in Patients With Small, Deep Hemispheric Infarction

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The reactivity of cerebral blood vessels to changes in PaCO₂ in areas of the cerebral cortex with or without diaschisis was investigated in 13 patients in a subacute or chronic stage after a small capsular infarct. A focal area of hypoperfusion (area of diaschisis) was detected in the ipsilateral sensorimotor cortex in each patient. Hyperventilation caused a significant reduction of regional cerebral blood flow in the area without diaschisis and only a tendency for regional cerebral blood flow to decrease in the area with diaschisis; CO₂ inhalation induced a slight increase in regional cerebral blood flow in the area without diaschisis and a significant increase in regional cerebral blood flow in the area with diaschisis. Regional cerebral blood flow reactivity to hypocapnia was significantly less in the area with diaschisis than in the area without, whereas the hypercapnic response was more marked in the area with diaschisis than in the area without. Our results suggest that in the area with diaschisis, the arterioles may be abnormally vasoconstricted at rest such that they cannot constrict further in response to hypocapnia but can dilate more during hypercapnia than in the area without diaschisis. This excessive resting vasoconstriction may result from decreased tissue elaboration of CO₂ due to local decrease of metabolic function. (Stroke 1988;19:840-845)

The concept that a local brain lesion could cause a transient depression of function in structurally normal areas distant from, but connected to, the originally involved site was called "diaschisis" by von Monakow. Pertinent observations have been reported, with additional documentation from advances in measurements of cerebral blood flow (CBF) and metabolism. The occurrence of interhemispheric diaschisis, intrahemispheric diaschisis, or crossed cerebellar diaschisis in different distant sites following a hemispheric infarction is now well established. The manifestations of these clinical entities have been attributed to the depression of neural function in other brain regions linked to the infarcted area and have been demonstrated to be hypometabolic regions.

In the last decade, the use of positron emission tomography (PET) to study stroke has confirmed the original observation relating to diaschisis. Several studies have investigated the relations among blood flow, oxygen metabolism, and glucose utilization and have demonstrated the proportional and parallel reductions in CBF and metabolism in the hemisphere or cerebellum contralateral to that in which diaschisis is manifested. Only a few reports have described the characteristics of the cerebral blood vessels in the area of diaschisis. The cerebral vascular tone or resistance and the vascular response to changes in mean arterial blood pressure (MABP) or arterial carbon dioxide tension (PaCO₂) remain unclear.

In our preliminary study, we reported on the cerebral vascular tone in the ipsilateral cerebral cortex, in which a small infarct in the internal capsule manifested a focal area of hypoperfusion. The purpose of our current study is to investigate the reactivity of cerebral blood vessels to PaCO₂ changes in areas of the cerebral cortex both with and without diaschisis, which result from a small, deep capsular infarct.
showed a small capsular infarct diagnosed as a moderate hemiparesis after cerebral infarct and hypodense lesion on computed tomography (CT scan). Informed consent was obtained from each subject before the initiation of the study in accordance with the Helsinki Declaration of 1975. Regional cerebral blood flow (rCBF) was measured in all patients using the 133Xe intra-arterial injection method. The size of the low-density capsular lesion was determined by measuring the diameter (mm) on the numeric printout of the CT scan. rCBF with subjects in the resting state ranged from 2.56 to 8.96 cm². No occlusive lesion was detected in the intracranial or extracranial arteries on serial cerebral angiograms. The details of these findings are presented in Table 1.

### Subjects and Methods

We studied 13 patients who suffered from mild or moderate hemiparesis after cerebral infarct and showed a small capsular infarct diagnosed as a hypodense lesion on computed tomography (CT scan). Informed consent was obtained from each subject before the initiation of the study in accordance with the Helsinki Declaration of 1975. Regional CBF (rCBF) was measured in all patients using the 133Xe intra-arterial injection method. The size of the low-density capsular lesion was determined by measuring the diameter (mm) on the numeric printout of the CT scan. rCBF with subjects in the resting state measured using our reported method showed a significant decrease in hemispheric CBF compared with normal controls and a focal hypoperfusion area around the central sulcus in all patients. This finding has been described. The area of hypoperfusion ranged from 2.56 to 8.96 cm². No occlusive lesion was detected in the intracranial or extracranial arteries on serial cerebral angiograms. The details of these findings are presented in Table 1.

### Measurement of Regional Cerebral Blood Flow

A small catheter was inserted into an internal carotid artery, and an Anger-type gamma camera (Dyna Camera 3C, Picker International, Inc., Cleveland, Ohio) was placed over the lateral (12 patients) or the ventral (one patient) aspect of the head. Arterial blood was sampled anaerobically, and arterial blood gases were analyzed using an automatic gas analyzer (model 175, Corning Glass Works, Corning, New York). Approximately 4 mCi of 133Xe in 2 ml saline was injected rapidly through the catheter. The y-rays were measured in 5-second periods successively for 130 seconds, processed into digital images on a 64 × 64 matrix of 4 × 4 mm² elements by an RI data processor (EDR-4200, Hitachi Medical Corp.), and recorded on magnetic tape. Arterial blood pressure was measured periodically with a mercuric manometer before and during this measurement. After 15 minutes, 11 patients were hyperventilated and six inhaled a 5% CO₂-air mixture through a mask for 5 minutes, during which time rCBF was measured again by injecting the same dose of 133Xe (immediately after collection of arterial blood for gas analysis) 3 minutes after the start of hyperventilation or CO₂ inhalation. Thereafter, angiography was carried out through the same catheter. For each rCBF measurement in these CO₂ manipulation studies, background activity was subtracted.

### Functional Image

The rCBF functional image was made up from the data recorded on the magnetic tape, as described elsewhere, and only a brief outline is given here. Data were processed in a 32 × 32 matrix arranged from the 64 × 64 matrix. Accordingly, a unit region consisted of the neighboring four elements (8 × 8 mm²). To eliminate the potential error that the data processing area contains areas of the gamma camera matrix that were not oriented toward the brain (e.g., the edge of the head), we defined the processing area for the rCBF functional image as unit regions that had >30% of the maximum count around the center of the accumulated image in the initial 10 frames after the injection of 133Xe. In our

### Table 1. Clinical Summary of 13 Patients With Small Capsular Infarcts

<table>
<thead>
<tr>
<th>No./age/sex</th>
<th>Interval (days)</th>
<th>Size (mm²)</th>
<th>PacO₂ (mm Hg)</th>
<th>Extent (cm²)</th>
<th>rCBF (ml/100 g/min)</th>
<th>Extent (cm²)</th>
<th>rCBF (ml/100 g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/70/M</td>
<td>14</td>
<td>9 × 6</td>
<td>41</td>
<td>65.92</td>
<td>49</td>
<td>3.84</td>
<td>41</td>
</tr>
<tr>
<td>2/39/M</td>
<td>18</td>
<td>16 × 12</td>
<td>43</td>
<td>69.12</td>
<td>46</td>
<td>2.56</td>
<td>39</td>
</tr>
<tr>
<td>3/58/M</td>
<td>18</td>
<td>6 × 6</td>
<td>35</td>
<td>69.76</td>
<td>43</td>
<td>5.76</td>
<td>31</td>
</tr>
<tr>
<td>4/34/F</td>
<td>21</td>
<td>8 × 6</td>
<td>42</td>
<td>77.44</td>
<td>52</td>
<td>4.48</td>
<td>42</td>
</tr>
<tr>
<td>5/44/M</td>
<td>28</td>
<td>20 × 12</td>
<td>34</td>
<td>74.88</td>
<td>37</td>
<td>5.12</td>
<td>22</td>
</tr>
<tr>
<td>6/33/F</td>
<td>45</td>
<td>10 × 7</td>
<td>43</td>
<td>71.04</td>
<td>52</td>
<td>3.20</td>
<td>37</td>
</tr>
<tr>
<td>7/72/M</td>
<td>51</td>
<td>27 × 15</td>
<td>40</td>
<td>78.08</td>
<td>38</td>
<td>4.48</td>
<td>29</td>
</tr>
<tr>
<td>8/61/M</td>
<td>55</td>
<td>10 × 5</td>
<td>39</td>
<td>80.64</td>
<td>53</td>
<td>3.20</td>
<td>45</td>
</tr>
<tr>
<td>9/57/M</td>
<td>64</td>
<td>29 × 15</td>
<td>36</td>
<td>77.44</td>
<td>41</td>
<td>2.56</td>
<td>34</td>
</tr>
<tr>
<td>10/70/M</td>
<td>110</td>
<td>7 × 7</td>
<td>39</td>
<td>71.68</td>
<td>42</td>
<td>5.12</td>
<td>34</td>
</tr>
<tr>
<td>11/53/M</td>
<td>120</td>
<td>12 × 8</td>
<td>41</td>
<td>62.72</td>
<td>40</td>
<td>8.96</td>
<td>29</td>
</tr>
<tr>
<td>12/55/M</td>
<td>120</td>
<td>14 × 10</td>
<td>31</td>
<td>74.24</td>
<td>36</td>
<td>3.84</td>
<td>29</td>
</tr>
<tr>
<td>13/78/M</td>
<td>120</td>
<td>10 × 9</td>
<td>38</td>
<td>67.20</td>
<td>58</td>
<td>3.84</td>
<td>49</td>
</tr>
<tr>
<td>Mean 58</td>
<td>64</td>
<td>39</td>
<td></td>
<td>72.32</td>
<td>45</td>
<td>4.38†</td>
<td>35†</td>
</tr>
<tr>
<td>SD 13</td>
<td>43</td>
<td>4</td>
<td></td>
<td>5.35</td>
<td>7</td>
<td>1.69</td>
<td>8</td>
</tr>
</tbody>
</table>

Interval, days from onset to rCBF measurement; size, low-density area on computed tomogram; PacO₂, arterial carbon dioxide tension; rCBF, regional cerebral blood flow; M, male; F, female.

*Gamma camera was placed over ventral aspect of the head.
†p < 0.01, ‡p < 0.001 (paired t test) significantly different from mean of area without diaschisis.
TABLE 2. rCBF and Size of Capsular Infarct in 13 Patients

<table>
<thead>
<tr>
<th>Low-density area on computed tomogram</th>
<th>rCBF (ml/100 g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Area without diaschisis</td>
</tr>
<tr>
<td>≤10 mm</td>
<td>50 ± 6</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>40 ± 4*</td>
</tr>
</tbody>
</table>

rCBF, regional cerebral blood flow. Patients were divided into groups according to largest diameter of low-density area presented in Table 1.

*p<0.01, †p<0.05 (unpaired t test) significantly different from mean rCBF in patients with smaller infarcts.

previous report,15 by superimposing the data processing area on 99mTc-brain scintigrams performed simultaneously, we confirmed that we could successfully delete the areas that were not oriented toward the brain. rCBF was calculated at every unit region in this data processing area by the initial slope method, and 0.87 was used as the 133Xe brain-blood partition coefficient. rCBF values for the corresponding unit regions were displayed on a cathode-ray tube as a gray map, with brightness modulation as the functional image. Numerical rCBF values in a map format were also displayed.

Data Analysis

Mean CBF (CBF) was determined from rCBF values in all regions. To find interregional differences in blood flow, the percent relative flow in each region was calculated as (rCBF - CBF)/CBFx 100. The regional variation in the rCBF functional image of controls without intracranial diseases, expressed as standard deviation (SD), was 7%.15 Therefore, in our present study, the region with a relative flow of less than -15% (>2x SD) was defined as the area of hypoperfusion. As reported,6 a focal hypoperfusion area was observed in all patients and localized around the central sulcus, and this focal hypoperfusion area was defined as the "area of diaschisis". CBF in this hypoperfusion area in the resting state was thus defined as rCBF in the area with diaschisis, and CBF in the remaining area of the rCBF functional image was defined as rCBF in the area without diaschisis.

As serial images were measured at the same position during hyperventilation or CO2 inhalation as in the resting state, regional hemodynamic changes could be analyzed by comparing rCBF of the same unit region in functional images before and after the test. The relations between blood flow and cerebral perfusion pressure in the brain regions were assessed by calculating cerebrovascular resistance (CVR) as MABP/rCBF, mm Hg/ml/100 g/min, with MABP used instead of the cerebral perfusion pressure. The PaCO2-rCBF relations were assessed by calculating the reactivity of cerebral vessels to CO2, as ΔrCBF/ΔPaCO2, ml/100 g/min/mm Hg. The value was positive if rCBF changed in the same direction as PaCO2; if the changes were in opposite directions, it was negative.

Results

There were no clear relations between interval from ictus to the rCBF measurement, the size of infarction on CT scan, the resting PaCO2, and the extent of areas with or without diaschisis. On the contrary, significant decreases of rCBF in areas both with and without diaschisis (p<0.01, p<0.05, respectively) were noted in patients with large infarcts compared with patients with smaller ones (Table 2).

Hemodynamic changes induced by hyperventilation in 11 patients are shown in Table 3. Following a short period of hyperventilation, MABP changed variably in each patient. The overall mean change of MABP was a slight nonsignificant decrease. Various reductions of PaCO2 were achieved in individual patients by this procedure, and mean ± SD PaCO2 decreased significantly (p<0.001), from 39 ± 4 to 32 ± 4 mm Hg. The global significant reduction of rCBF in the large area without diaschisis was seen in all patients, and mean ± SD rCBF decreased significantly (p<0.001) from 44 ± 6 to 33 ± 7 ml/100 g/min. However, small decreases of rCBF in seven of the 11 patients, no change in one patient, and even an increase of rCBF in the remaining three patients were seen in the small area with diaschisis. Mean rCBF in the area with diaschisis decreased slightly (not significant). The area with diaschisis observed in the resting rCBF functional image disappeared in eight of the 11 patients upon hyperventilation. Aside from these, there were no regions with relative flow of less than -15% in the functional image during hyperventilation.

TABLE 3. Effect of Hyperventilation and CO2 Inhalation in Patients With Small Capsular Infarcts

<table>
<thead>
<tr>
<th></th>
<th>MABP (mm Hg)</th>
<th>PaCO2 (mm Hg)</th>
<th>rCBF (ml/100 g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td></td>
<td>Area without diaschisis</td>
</tr>
<tr>
<td>Resting state</td>
<td>11</td>
<td>112±12</td>
<td>39±4</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>11</td>
<td>110±7</td>
<td>32±4†</td>
</tr>
<tr>
<td>Resting state</td>
<td>6</td>
<td>122±18</td>
<td>38±2</td>
</tr>
<tr>
<td>CO2 inhalation</td>
<td>6</td>
<td>118±8</td>
<td>41±2‡</td>
</tr>
</tbody>
</table>

MABP, mean arterial blood pressure; PaCO2, arterial carbon dioxide tension; rCBF, regional cerebral blood flow. Values are mean ± SD.

*p<0.001, †p<0.05 (paired t test) significantly different from mean in area without diaschisis.

f p<0.001, †p<0.01 (paired t test) significantly different from mean of corresponding resting state.
As also shown in Table 3, CO₂ inhalation variously changed MABP in each patient. Mean MABP changes were not significant. Although the elevation of Paco₂ was small in some patients who were anxious during CO₂ inhalation and who might have had a leak from the mask in the gas administering system, a significant increase in Paco₂ was induced, from 38 ± 2 mm Hg in the resting state to 41 ± 2 mm Hg during CO₂ inhalation. The overall rCBF increased in the area without diaschisis in all six patients, whereas the elevation of the mean was not significant. rCBF in the area with diaschisis increased remarkably without exception. Mean ± SD rCBF changed significantly (p<0.01), from 37 ± 8 to 50 ± 12 ml/100 g/min. The area with diaschisis remained in the rCBF functional image of one of the six patients during CO₂ inhalation.

CVR in the areas with and without diaschisis before and after hyperventilation and CO₂ inhalation is shown in Table 4. In the resting state, CVR increased in the area without diaschisis in all six patients, whereas the elevation of the mean was not significant. CVR in the area with diaschisis increased remarkably without exception. Mean ± SD CVR in the area with diaschisis increased significantly (p<0.01), from 3.41 ± 0.91 to 4.44 ± 0.48 ml/100 g/min/mm Hg. The index was positive in the area without diaschisis in all six patients, but significant increase was noted only in the area without diaschisis. In six patients, CO₂ inhalation reduced CVR in both areas, but significant reduction of CVR was observed only in the area with diaschisis.

Table 5 shows the index for cerebral vascular reactivity to CO₂ in the areas with and without diaschisis by functional activation with hyperventilation or CO₂ inhalation. On hyperventilation in 11 patients, the change in rCBF per unit reduction of Paco₂ was significantly greater in the area without diaschisis than in the area with diaschisis. The index was positive in the area without diaschisis in all 11 patients, whereas in the area with diaschisis the index was positive in seven of 11, 0 in one, and negative in the other three patients. With CO₂ inhalation in six patients, the index was positive in both areas in all patients. The mean index was smaller in the area without diaschisis than in the area with diaschisis, though this difference was not significant.
obtain information on the cortical circulation in the infarcted hemisphere. Such information was available with the two-dimensional $^{133}$Xe method. The small size and shallow depth of the infarcted area made it possible to disregard regional differences of the $^{133}$Xe partition coefficient and a "look-through" artifact. With intracarotid injection of $^{133}$Xe, a high count rate could be reached to obtain high spatial resolution so that the rCBF functional images appeared to have high enough accuracy in the clinical diagnosis. Our system adopted the initial slope method to calculate rCBF, which made it suitable to observe hemodynamic changes by various physiological tests.

In our study, we showed significant differences between cerebrovascular reactivity to PaCO$_2$ changes in the areas of cerebral cortex with and without diaschisis, independent of the accompanying changes in systemic blood pressure. The mechanism of chemical control of rCBF in the territory without diaschisis appeared close to normal, whereas the reactivity of blood vessels to CO$_2$ changes seemed abnormal in the area with diaschisis. It has been suggested that bilateral reduction of CBF in patients with unilateral infarction may be caused by a diffuse increase in CVR. As presented in Table 4, in the ipsilateral hemisphere CVR in the resting state was significantly greater in the area with diaschisis than in the area without diaschisis. Using the $^{133}$Xe intracarotid injection method in patients with ischemic cerebrovascular disease, Ackerman et al.$^{10}$ examined the rCBF response to hypocapnia induced by hyperventilation in the ipsilateral hemisphere. They found that a positive linear correlation was demonstrated between CO$_2$ reactivity and conductance (the reciprocal of resistance). We found that the higher the initial CVR, the smaller the change in CBF occurred with hypercapnia. However, this could not explain the paradoxical rCBF elevations in the area with diaschisis in some patients during hyperventilation. Such a paradoxical response was previously observed in patients with acute cerebral infarction by Melamed et al.$^{11}$ who suggested that vasoparalysis may be present in areas with diaschisis both early and late after stroke.

When cerebral perfusion pressure changes, arteries with a diameter of $\geq 50$ $\mu$m act under nervous control while those with a smaller diameter act under chemical control in proportion to the level of local metabolism, thus balancing each other to regulate local circulation.$^{20,21}$ Contrary to our results, Fujishima et al.$^{22}$ reported that the lower the cerebral oxygen consumption, the lower the capacity of cerebral vessels to dilate in response to a PaCO$_2$ increase. It seems that the difference depends on the degree of pathologic damage in the brain tissue in which CO$_2$ reactivity is assessed. They assessed reactivity in the whole hemisphere, which contained the infarcted lesion, whereas we studied structurally normal brain tissue. On the other hand, Wise et al.$^{8}$ described in a PET study that, in spite of sufficient availability, both oxygen and glucose consumption in the corresponding regions of the contralateral hemisphere (where diaschisis is believed to occur) are slightly lower than those of normal controls. The low consumption of oxygen and glucose may lead to a reduction of CO$_2$ production in the area affected by diaschisis. In these areas, arterioles may hence tend to constrict, limiting further constriction in response to hypocapnia but allowing more vasodilatory reserve during hypercapnia.

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References


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