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.1 Pertinent observations2-5 have been reported, with additional documentation from advances in measurements of cerebral blood flow (CBF) and metabolism. The occurrence of interhemispheric diaschisis,3,4 intrahemispheric diaschisis,5,6 or crossed cerebellar diaschisis7 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.8

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Supported in part by a grant from the Daiwa Health Foundation, Tokyo, Japan.

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Received September 4, 1986; accepted March 4, 1988.

In the last decade, the use of positron emission tomography (PET) to study stroke has confirmed the original observation relating to diaschisis. Several studies9-11 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 reports12,13 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,14 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.
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 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.

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>Area without diaschisis</th>
<th>Area with diaschisis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Extent (cm²)</td>
<td>rCBF (ml/100 g/min)</td>
</tr>
<tr>
<td>1/70/M</td>
<td>14</td>
<td>9 x 6</td>
<td>41</td>
<td>65.92</td>
<td>49</td>
</tr>
<tr>
<td>2/39/M</td>
<td>18</td>
<td>16 x 12</td>
<td>43</td>
<td>69.12</td>
<td>46</td>
</tr>
<tr>
<td>3/58/M</td>
<td>18</td>
<td>6 x 6</td>
<td>35</td>
<td>69.76</td>
<td>43</td>
</tr>
<tr>
<td>4/34/M</td>
<td>21</td>
<td>8 x 6</td>
<td>42</td>
<td>77.44</td>
<td>52</td>
</tr>
<tr>
<td>5/44/M</td>
<td>28</td>
<td>20 x 12</td>
<td>34</td>
<td>74.88</td>
<td>37</td>
</tr>
<tr>
<td>6/53/F</td>
<td>45</td>
<td>10 x 7</td>
<td>43</td>
<td>71.04</td>
<td>52</td>
</tr>
<tr>
<td>7/72/M</td>
<td>51</td>
<td>27 x 15</td>
<td>40</td>
<td>78.08</td>
<td>38</td>
</tr>
<tr>
<td>8/61/M</td>
<td>55</td>
<td>10 x 5</td>
<td>39</td>
<td>80.64</td>
<td>53</td>
</tr>
<tr>
<td>9/57/M</td>
<td>64</td>
<td>29 x 15</td>
<td>36</td>
<td>77.44</td>
<td>41</td>
</tr>
<tr>
<td>10/70/M</td>
<td>110</td>
<td>7 x 7</td>
<td>39</td>
<td>71.68</td>
<td>42</td>
</tr>
<tr>
<td>11/53/M</td>
<td>120</td>
<td>12 x 8</td>
<td>41</td>
<td>62.72</td>
<td>40</td>
</tr>
<tr>
<td>12/65/M</td>
<td>120</td>
<td>14 x 10</td>
<td>31</td>
<td>74.24</td>
<td>36</td>
</tr>
<tr>
<td>13/78/M</td>
<td>120</td>
<td>10 x 9</td>
<td>38</td>
<td>67.20</td>
<td>58</td>
</tr>
<tr>
<td>Mean 58</td>
<td>64</td>
<td>39</td>
<td>5.35</td>
<td>7</td>
<td>3.55</td>
</tr>
<tr>
<td>SD 13</td>
<td>43</td>
<td>4</td>
<td>3.84†</td>
<td>35†</td>
<td></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.

tp<0.01, tp<0.001 (paired t test) significantly different from mean of area without diaschisis.

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 x 64 matrix of 4 x 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 x 32 matrix arranged from the 64 x 64 matrix. Accordingly, a unit region consisted of the neighboring four elements (8 x 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
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>Condition</th>
<th>n</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></td>
<td>Area without diaschisis</td>
<td>Area with diaschisis</td>
<td>Area without diaschisis</td>
</tr>
<tr>
<td>Resting state</td>
<td>11</td>
<td>112 ± 12</td>
<td>39 ± 4</td>
<td>44 ± 6</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>11</td>
<td>110 ± 7</td>
<td>32 ± 4*</td>
<td>33 ± 7†</td>
</tr>
<tr>
<td>Resting state</td>
<td>6</td>
<td>122 ± 18</td>
<td>38 ± 2</td>
<td>46 ± 8</td>
</tr>
<tr>
<td>CO₂ inhalation</td>
<td>6</td>
<td>118 ± 8</td>
<td>41 ± 2‡</td>
<td>55 ± 14</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.
‡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 vari-
ously changed MABP in each patient. Mean MABP
changes were not significant. Although the eleva-
tion 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 in-
creased 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 inhala-
tion is shown in Table 4. In the resting state, CVR
in the area with diaschisis was significantly (p < 0.01)
greater than in the area without diaschisis. In 11
patients, hyperventilation elevated CVR in both
areas, but significant increase was noted only in the
area without diaschisis. In six patients, CO₂ inhala-
tion 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 hyperven-
tilation 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.

**Discussion**

A normal brain has the intrinsic ability for the
cerebral blood vessels to alter their caliber to main-
tain a constant blood flow with variations in blood
pressure.16 At the same time, normal cerebral tissue
has the means for dynamic regulation of blood flow
in accordance with regional metabolic demands
depending on neural activity.17 Such regulation of
cerebral circulation is at least in part mediated by
the products of cerebral metabolism. CO₂, a meta-
abolic product, affects blood flow in the brain as a
whole, regionally altering the resistance of the cere-
bral vessels. The capacity of the vessels to dilate
when PaCO₂ increases and to constrict when it
decreases (i.e., chemical control) is reflected in the
change in CBF for a given change in PaCO₂. Many
structural and functional components in the brain
operate under these conditions of cerebral circula-
tion and cooperate with each other through neural
pathways to maintain integrated function of the
central nervous system. If damage occurs in one
part of the brain, lack of normal afferent input may
induce a neural hypoactivity in the target struc-
tures. The longer such a condition remains, the
more likely will regulation of the cerebral circula-
tion be disturbed, possibly resulting in morphologic
alterations.8 Therefore, it seems of interest to inves-
tigate whether such chemical control is disturbed in
the brain regions in which diaschisis occurs. In our
study, 13 patients with small capsular infarcts were
investigated in a subacute or chronic stage, when
intrahemispheric diaschisis is observed.6

There are several methods for studying regional
blood flow or metabolic function in the brain.18 Our
current data for rCBF was obtained by the 133Xe
intracarotid injection method. This approach neces-
sitates puncture of the carotid artery and usually
restricts CBF examination to the carotid artery
territory in one hemisphere. Reliability of the rCBF
values in areas of the lesion remains uncertain
because the calculation depends on the 133Xe brain–
blood partition coefficient, which may change in
injured tissue. rCBF values in injured tissue may be
partially averaged with those in more normal, adja-
cent tissues. However, the limitations mentioned
above did not interfere with application of this
technique to our patients because our aim was to
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 physiologic 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$^{19}$ 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 hyperventilation. 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$^{13}$, who suggested that vasoparalysis may be present in areas with diaschisis both early and late after stroke.

When cerebral perfusion pressure changes, arterioles with a diameter of ≥50 μm 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.$^{23}$ 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.

Acknowledgments

The authors wish to thank Dr. H. Abe (National Osaka Hospital) and Dr. T. Nukada (National Osaka South Hospital) for their constant interest and guidance in this investigation and Miss K. Nishikawa and Miss E. Tsugawa for their secretarial assistance.

References


**KEY WORDS** • carbon dioxide • cerebral blood flow • cerebral infarction • metabolism
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Stroke. 1988;19:840-845
doi: 10.1161/01.STR.19.7.840

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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